The Role of Personality Disorders, Perceived Stress, and Cognitive Vulnerability on Treatment Outcome in Major Depressive Disorder

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TABLE OF CONTENTS

ABSTRACT

Personality disorders (PD) — conditions characterized by enduring and pervasive dysfunctional patterns of cognition, affect, and interpersonal relations — are often observed in individuals afflicted by major depressive disorder (MDD). Although the co-occurrence PD has been associated with poor treatment outcome in MDD, little is known about mechanisms mediating this link. A review of extant literature led to the hypothesis that PD vulnerability, cognitive vulnerability, and stress exacerbation negatively influence treatment outcome in major depression. To directly test this hypothesis, we conducted two empirical studies evaluating perceived stress and maladaptive cognitions in 384 MDD outpatients enrolled in an 8-week open-label treatment of fluoxetine. In Study 1, multiple regression analyses revealed that the presence of stable Cluster A, but not Cluster B or C, pathology was uniquely associated with higher levels of perceived stress after pharmacological treatment. This finding suggested that stress exacerbation might be a critical factor associated with poor treatment outcome in MDD subjects with Cluster A pathology. In Study 2, structural equation modeling and path analyses revealed that the effect of PD vulnerability on treatment outcome was fully mediated by increased pre-treatment cognitive vulnerability and depression severity, which led to increased stress perception after treatment and poorer antidepressant response. Collectively, findings of the present studies highlight important mediating variables (cognitive vulnerability and stress appraisal) that might explain links between PD comorbidity and poor course and treatment of MDD and might help to resolve inconsistencies in the literature.

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GENERAL INTRODUCTION

Major depressive disorder (MDD) is a severe and multifaceted mental illness that is characterized by depressed mood and loss of pleasure, neurovegetative symptoms (e.g., disturbances in sleep and appetite), negative cognitive distortions (e.g., excessive guilt and feelings of worthlessness), and disrupted psychomotor activity (e.g., agitation or retardation) (APA, 2000). Both in terms of personal suffering and socioeconomic strain, depression is now regarded as a substantial public health problem. Recent epidemiological studies indicate that prevalence rates for depression exceed most other psychiatric disorders; the lifetime prevalence rate in the U.S. is approximately 17% (Blazer et al., 1994; Kessler et al., 2005). Highlighting the severity of the problem, the World Health Organization Global Burden of Disease Study identified depression as the most burdensome disease in the world with regard to disability-adjusted life years among people in the middle years of life (Murray and Lopez, 1996). It is estimated that the debilitating effects of depression result in worldwide losses of 13 million dollars each year, with 1.5 million of those in the U.S. alone (Greden, 2001; Sartorius, 2001; Ustun et al., 2001).

Depression is severe not only in terms of symptomology, but also in terms of chronicity. Over 75% of depressed patients have more than one depressive episode, and relapses often occur within 2 years of recovery from a previous episode (Keller and Bobland, 1998). The high relapse rate in depression calls attention to the need for a better understanding of specific factors that increase people's risk for developing repeated episodes of this debilitating disorder.

Among the various risk factors associated with MDD, four have been most consistently linked with increased vulnerability to depression (Fava and Kendler, 2000): *gender*, *stressful life events*, *adverse childhood experiences*, and *certain personality traits*. Several studies have found that women are about twice as likely as men to develop a unipolar mood disorder (either dysthimia or major depression). According to the National Comorbidity Study, for example, the lifetime prevalence of MDD in the US population was 21.3% for women versus 12.7% for men (Blazer et al., 1994). In the US this sizable gender difference first appears in adolescence and remains until about age 65 (Nolen-Hoeksema and Ahrens, 2002). Similar differences in rates of depression between male and females have been described in many countries around the world.

A number of stressful life events increase the risk for depression and have unfavorable effects on treatment outcomes. Social and environmental stressors associated with increased risk for MDD include job loss, marital difficulties, and loss of close personal relationships (Brown and Harris, 1989; Kendler et al. 1999; Kessler, 1997; Tennant, 2002). In addition to more immediate stressors, a range of early (distal) adversities, particularly during childhood, have been identified as risk factors for depression later in life. Physical and sexual abuse, dysfunctional parent-child relationships, parental discord, and early maternal loss are among the early adversities most consistently associated with the later development of depression (Brown and Harris, 1989; Fava and Kendler, 2000).

Although increased vulnerability to depression has been linked to proximal and distal stressors, it is clear that only a portion of individuals who experience these life stressors go on to develop depression. Diathesis-stress models have accounted nicely for this

phenomenon by postulating that specific preexisting vulnerabilities might predispose some individuals to depression when confronted with negative life stress, while others without such diatheses are at low risk for depression, even in the face of comparable stressors (Gotlib and Hammen, 2002). Two diatheses that have received considerable attention are specific personality traits and cognitive vulnerabilities. With regard to broad personality factors, neuroticism has been most consistently established as a risk factor for depression. Neuroticism is a stable and heritable trait characterized by proneness to negative emotion, affective instability, and overreaction in response to stress and adverse events (Kendler et al., 2006; Munafo et al., 2006; Roberts and Kendler, 1999). Cognitive theories of depression, on the other hand, point to an individual's interpretation of negative events as a risk factor for the development and maintenance of depression (Abramson et al., 1989; Beck, 1967). Beck's cognitive theory of depression, in particular, highlights the role of dysfunctional attitudes in the onset of depression. Such attitudes include inflexible and unrealistic beliefs about the self, the future, and the world, and often involve themes of deriving one's worth from being perfect or needing approval from others. Beck proposes that these maladaptive cognitive biases are activated in response to specific stressors and lead to an increased vulnerability to depression (Beck et al., 1979).

Other risk factors have been associated with depression as well, although their causal role is less established (Fava and Kendler, 2000). These include low socioeconomic status, low levels of social support, and being separated or divorced. In the ECA study, for example, people who were separated or divorced had higher 1-year prevalence rates of major depression (6.3%) than did those who were never married (2.1%), currently

married (2.1%), or widowed (2.1%)., A sizeable proportion of couples experiencing marital distress have a partner with clinical depression, indicating the likelihood of a bidirectional relationship between depression and marital difficulties. Moreover, there are high correlations between marital dissatisfaction and depression for both men and women (e.g., Beach and Jones, 2002, Whisman, et al., 2004). In addition, for those who have emerged from a depressive episode, marital distress and dissatisfaction are associated with increased risk for relapse. (Butslaff and Hooley, 1998; Hooley and Teasdale, 1989).

A final variable that has been associated with both increased risk for and persistence of depression is comorbity (the co-occurrence of depression with other forms of psychopathology). Among the most widely studied disorders that co-occur with depression are the personality disorders (PD), which are characterized by profoundly entrenched and inflexible patterns of relating, perceiving, and thinking (APA, 2000). In general, PD comorbidity in major depression has been associated with adverse effects on the course and treatment of MDD (e.g., Pilkonis and Frank, 1988; Hart et al., 2001; Cyranowski et al., 2004; Riso et al., 1996; Shea et al., 1990; Peselow et al., 1992).

Although PD comorbidity has been linked to poor treatment outcome in depression, little is known about putative mechanisms mediating this link. The overarching goal of the present studies is to investigate the potential role on treatment outcome in depression of three variables that have been linked to increased vulnerability to depression: perceived stress, cognitive vulnerability, and personality vulnerability. Two studies involving assessment of a large sample of MDD outpatients (N = 227) before and after an

8-week open-label treatment with fluoxetine were designed to answer the following research questions:

Study 1. Is the presence of a specific PD associated with elevated levels of stress appraisal after antidepressant treatment, which might constitute a vulnerability factor for future relapse? In Study 1, multiple linear regression analyses were used to test the hypothesis that PD comorbidity might affect the course of MDD by modulating factors that increase the overall risk of depression, including an elevated tendency to perceive stress.

Study 2. Do PD vulnerability, cognitive vulnerability, and stress exacerbation influence treatment outcome in MDD? In Study 2, structural equation modeling and path analyses were used to test causal relations among personality vulnerability, cognitive vulnerability, perceived stress and treatment outcome. Specifically, we hypothesized that: (1) certain personality traits would be associated with increased cognitive vulnerability; (2) cognitive vulnerability would lead to increased stress appraisal after the treatment; and (3) increased stress appraisal would lead to poor treatment outcome.

In combination, these studies suggest that (1) the presence of PD comorbidity is associated with elevated stress appraisal after antidepressant treatment; and (2) the effect of PD vulnerability on treatment outcome is fully mediated by increased pre-treatment cognitive vulnerability, which led to increased stress perception after treatment and poorer antidepressant response. Thus, stress exacerbation and depressogenic cognition appear to be important factors linked to poor treatment outcome in MDD subjects reporting enduring Axis II pathology.

In **Section I**, a review of a large body of literature linking stress and depression will be presented. Thereby, we will emphasize: (1) The role of episodic and chronic stress in the etiology and maintenance of depression; (2) putative mechanisms underlying depression-stress relations; (3) methodological issues in stress assessment; (4) the role of cognitive vulnerability in the etiology of depression; and (5) possible interactions among cognitive vulnerability, stress, and depression. In **Section II**, a review of literature pertaining to personality disorders will be provided. This selective review will emphasize: (1) categorical vs. dimensional approaches to PD classification and conceptualization; (2) treatment implications of MDD-PD comorbidity; (3) various etiological models underlying this comorbidity; and (4) the potential role of personality styles in conferring risk to depression. Section II concludes with a brief discussion about how depression, stress, and personality pathology might interact. In **Section III**, two empirical studies investigating the role of PD comorbidity, stress appraisal, and cognitive vulnerability on treatment outcome in major depression will be presented. Finally, in **Section IV**, a general discussion of the present findings and their implications for current conceptualization of depression and its treatment will be presented.

I. DEPRESSION, STRESS, AND COGNITIVE VULNERABILITY

> *"The experience of depression is like falling into a deep, dark hole that you cannot climb out of. You scream as you fall, but it seems like no one hears you. Some days you float upward without even trying; on other days, you wish that you would hit bottom so that you would never fall again. Depression affects the way you interpret events. It influences the way you see yourself and the way you see other people."*
>
> [Barlow and Durand, 2005, p. 205]

1. Stress and Depression: Stressor Types

A large body of work has highlighted a key role of stress in the etiology and maintenance of depression (Kendler et al., 1999; Brown and Harris, 1989; Hammen, 2005; Monroe and Hadjiyannakis, 2002). In a recent review of the literature, Mazure (1998) concluded that major life events preceded 80% of depressive episodes and that stressors were 2.5 more likely in individuals with MDD than in healthy comparison subjects. Critically, stress has also been associated with poor treatment outcome and higher rates of relapse (Tennant, 2002).

While empirical evidence indicates that the majority of major depressive episodes are preceded by stressful events (Hammen, 2005), it is important to note the complexity of the interaction between stress and depression. For example, as the number of previous episodes of MDD increases, the relationship between stressful life events and depressive episode onset weakens (Mazure, 1998; Daley et al., 2000). Moreover, certain types of

stressors have been found to have unique impacts on the onset and course of depression. In the following section, this evidence will be reviewed.

1.1. Episodic Stress

Episodic stressors are discrete negative events with clear beginning and end points. These types of stressors have received the most empirical attention in the literature on stress and depression. Methodologically, the association between episodic stress and depression has been investigated through counts and ratings of stressful events, accumulated across content category and time. Interestingly, the great majority of life events leading to the onset of depression have been found to occur during the first month after the stressful events (Kendler et al. 1998).

Empirical evidence suggests, however, that *content* of stressful events plays a significant role in the onset of depression. Specifically, stressors characterized by interpersonal loss, including bereavement, separation and ending, have been most consistently associated with depression (Paykel and Cooper, 1992; Tennant, 2002). Brown et al. (1995) expanded the concept of loss events beyond the interpersonal domain to include loss of self-esteem, loss of role, and loss of cherished ideas.

In addition to content, studies have shown that the degree of personal involvement in the generation of stressful events moderates the relationship between stress and depression. Kendler and coworkers (1999), for example, found that *dependent events*, stressful events to which the person actively contributed, were better predictors of the onset of depression than were independent (e.g. fateful) events.

1.2. Chronic Stress

While specific types of episodic stress have been empirically linked to the onset of depression, research indicates that chronic stress (e.g., stress that lasts for more than 12 months) may be a stronger predictor of depressive symptoms than discrete stressors (McGonagle and Kessler, 1990). Early studies have found that persistent adverse conditions such as poverty, medical disability, and continued marital discord were linked to increased risk for depression (Brown and Harris, 1978; Dohrenwend et al., 1992). Although a link between chronic stress and depression has emerged as a robust trend in the literature, it is important to note that chronic stress has been defined using different terms across a number of studies. Paykel and Cooper (1992), for example, defined chronic stress as the absence of social support (which is actually *one example* of chronic stress); lack of support was found to increase vulnerability to depression. Hammen et al. (1992), on the other hand, found that interpersonal difficulties, especially in the contexts of family and close friendships, increased the risk for onset of depression if they lasted for more than six months.

In addition to definitional issues, the field has debated whether chronic stress may increase the risk for *chronic depression*. While some authors have observed such a relationship (Riso et al., 2002), others have argued that establishing a causal relationship between these two variables is challenging due to the difficulty of determining the timing of both chronic stress and chronic depression (Kessler, 1997).

Another important question concerns the potential association between chronic and episodic stress as they precipitate depression. Some studies have hypothesized that chronic stress serves to magnify the effect of episodic stress on MDD, a process referred

to as events "matching ongoing condition" (Brown and Harris, 1978). Surprisingly however, other studies have reported a negative correlation between chronic and episodic stress (McGonagle and Kessler 1990), even finding that chronic stress reduced the negative effects of acute stress on depressive symptoms. A similar association was reported by Cairney et al. (2003), who observed that acute stressors predicted major depression only in married mothers, not in the single mothers who likely experienced higher levels of chronic stressors. It may be that single mothers become habituated to chronic stress, making them less reactive to co-occurring episodic stress.

2. Stress and Depression: Underlying Mechanisms

In the previous section, evidence was summarized indicating that episodic stress often predicts depression and plays a causal role in many instances of MDD. In the following sections, various conceptualizations of stress-depression relations will be described.

2.1 Kindling/sensitization Model

Post (1992) postulated a kindling/sensitization model to investigate possible mechanisms linking stress and depression. In this model, repeated stressors and subsequent episodes of depression lead to neurobiological changes that make a person sensitized or "kindled". As a consequence of these changes in the brain, the onset of mood disorder episodes becomes increasingly independent of external stressors, and patients become progressively more likely to experience spontaneous episodes. Support for the kindling hypothesis was provided by Kendler et al. (2001) in their study of almost

2,400 women. These authors found that an increase in the number of depressive episodes predicted a reduced association between life events and onset of depression (see Ehnvall and Agren, 2002 for a replication).

Intriguingly, Kendler et al. (2001) also found that the association between stressful life events and depression was weak when genetic vulnerability for MDD was high. These patients can be characterized as "prekindled," as the effect of the genetic diathesis was similar to the effect that three depressive episodes had on those individuals with low genetic risk for depression. Based on these findings, the Kendler et al. suggested that two distinct pathways can lead to a kindled (or sensitized) state in which stressors play a restricted role in triggering depressive disorders: (1) the repeated experience of depressive episodes in subjects with low genetic vulnerability to depression; or (2) a preexisting genetic vulnerability to the disorder.

2.2. Stress Generation

In recent years, assessments of bidirectional mechanisms linking stress and depression and the role of the individual in eliciting stressors have attracted considerable attention. In an early study, Hammen (1991) observed that patients with recurrent depression experienced high level of stressful events, and suggested that such individuals play an active role in producing negative life events. Consistent with this "stress generation" theory, Hammen (1991) and several other investigators (e.g., Daley et al., 1997; Patton et al., 2003; Harkness and Luther, 2001) have found that subjects with a history of depression experience more dependent, but not independent (i.e., fateful), stressors, compared to control subjects. Dependent events associated with interpersonal

issues were particularly prominent in the lives of those with recurrent depression. Harkeness et al. (1999) extended these findings in a comparison of depressed outpatients with recurrent depression versus first onset depressives. Those with recurrent depression reported significantly more dependent stressors in the past year, suggesting the possibility of a progressive stress generation effect.

, These findings are important from a clinical perspective because dependent-type interpersonal stressors are common precipitating factors in depression (Hammen et al., 1985; Kendler et al., 1999). Thus, exposure to stress might lead to recurrence of depression due to a self-maintaining cycle.

In light of these bidirectional links between stress and depression, it becomes critical to investigate those factors that might contribute to stress generation. Several sociodemographic, clinical, and personality variables have been identified (Hammen, 2005). First, early-onset and pervasive *characteristics* (including attachment style, beliefs, values, expectations, traits, learned behaviors, and problem-solving styles) might contribute to stress generation. Second, an individual's interpersonal *context* - including mate selection, marital satisfaction, parenting behaviors, and children's characteristics - might increase the likelihood of experiencing dependent stressful events. Consistent with this notion, Hammen and Brennan (2002) have argued that women suffering from depression are often "trapped" in highly stressful family environments featuring marital discord and psychological/behavioral disorders in partners and offspring. Third, *situational characteristics*, including inadequate income, health problems, lack of education, and dissatisfaction with work, increase one's risk for experiencing stressful life events (e.g., Fergusson et al., 1997).

Finally, and of primary importance for the present study, personality variables have been linked to more frequent occurrence of dependent events, which in turn may increase risk for later depressive episodes. For example, Daley et al. (1997) found that depressed subjects with a comorbid disorder experienced higher levels of dependent stressful events compared to depressed subjects without a comorbid disorder. In particular, the presence of Cluster A (schizoid, paranoid, schizotypal personality disorder) and Cluster B (antisocial, borderline, histrionic, and narcissistic personality disorder) pathology predicted the frequency of dependent stressful events, which in turn predicted subsequent depressive episodes (Daley et al., 1998).

Additional variables that might increase the occurrence of dependent events, and thus confer increased vulnerability to depression, have been identified. In a longitudinal study, Davila and colleagues (1995) found that *poor social problem-solving skills* predicted the occurrence of interpersonal stress. These findings were later replicated by Herzberg et al. (1998), who found that low interpersonal competence predicted interpersonal stress one year later.

Traits associated with interpersonal functioning, particularly *autonomy* and *neuroticism*, have also been empirically linked to higher frequencies of stressful life events. Daley et al. (1997), for example, found that autonomy - a trait characterized by high valuing of achievement, independence, self-reliance, and assertiveness - predicted later dependent and stress and interpersonal conflict., Neuroticism has also been identified as a strong predictor of stress, particularly stress related to interpersonal life events (Kendler et al., 2003).

In sum, stress has been identified as an important predictor of the development and maintenance of depression. However, empirical evidence indicates that the relationship between stress and depression should be best conceptualized as bidirectional. Specifically, numerous studies have found that factors such as a history of depression and PD comorbidity increase the likelihood of stressful life events. These episodes of stress may, in turn, predispose individuals to future episodes of depression.

3. Stress and Depression: Moderators and Mediators

In previous sections, empirical evidence linking stress and depression was summarized. Although the link between stress and depression has received considerable support, it is clear that only a portion of individuals exposed to acute and chronic stressors experience depression. In the following section, biological, developmental, psychological/personality variables that might moderate the influence of stress on depression will be described.

3.1. Biological Moderators and Mediators

The dysregulation of biological stress mechanisms has been considered to be one of the key causes of depression (Holsboer, 1995; Thase et al., 2002). Abnormalities in the hypothalamic-pituatary-adrenal axis (HPA), in particular hypercortisolism, have been linked to the onset and perpetuation of depressive symptoms (Ehlert et al., 2001; Gold and Chourous, 2002). It has been postulated that the prolonged hypersecretion of cortisol due to chronic and/or episodic stress might contribute both to depressive symptoms and also to hippocampal atrophy due to neuronal cell death (Lee et al., 2002).

Recent research has also demonstrated that early adverse experiences can lead to HPA abnormalities that leave affected individuals sensitized to later stressful events. In an influential study in this area, Heim and coworkers showed that women who had experienced childhood sexual abuse exhibited exaggerated ACTH and cortisol releases in response to a laboratory stressor (see Heim et al., 2004 for a recent review). In a longitudinal study, Harris and coworkers (2000) found that relatively high morning cortisol levels, stressful life events, low self-esteem, and relationship problems predicted later depression onset. Although the precise nature of the relationship between HPA axis abnormality and depression still needs clarification, and inconsistent findings have been reported (e.g., Young et al., 2000), it may be that hypercorticolism renders the brain more susceptible to the effects of stress.

Interestingly, recent findings indicate that the effects of stressors on depression might be greatest for those individuals at high genetic risk for depression. In an influential paper, Caspi et al. (2003) showed that a polymorphism (short allele) in the promoter region of the serotonin transporter (5-HTTLPR) gene was linked to elevated depression in interaction with number of life stressors. This *gene x environment interaction* has been replicated recently by other investigators (Kaufman et al., 2004; Kendler et al., 2001; Taylor et al., 2006). Jacobs et al. (2006) also found that stressful life events exerted a larger depressogenic effect on women with 2 short (S) alleles; however, these authors found that the effect disappeared after adjusting for the influence of neuroticism on stressful life events. It may be that neuroticism, which is heritable and involves exaggerated responses to stress, mediates the *gene x environment interactions* described above.

3.2. Developmental Moderators and Mediators

Empirical evidence indicates that early stressors have an important effect on reactivity to future stress. Specifically, studies have shown that distal stressors can exacerbate the effects of chronic and episodic stress and act as diatheses that lower the threshold for stressors precipitating depression (Hammen, 2005). Early studies by Brown and Harris (1978) established that the effects of more current stressful events could be intensified by the loss of the mother during childhood. More recent research by Ensel et al. (1996) has also demonstrated that distal stressors (i.e., occurring before the age of 15) predict depressive symptoms in adulthood. Bifulco and coworkers (2000) illuminated a potential mechanism behind such findings by showing that early adversity might lead to increased risk for depression through its positive association with adult life stressors. Specifically, the authors found that women who endured neglect and abuse during childhood went on to experience high levels of severe adverse events in adulthood.

In a complementary line of work, Hammen and coworkers (2000) showed that less severe current stress was required to precipitate a depressive episode for women reporting childhood adversity compared to women with relatively stable childhoods. Thus, early experiences with adversity appear to moderate the link between current stressful events and depression via a process of "sensitization".

3.3. Psychological and Personality Moderators and Mediators

Theorists from a variety of paradigms have suggested that personality or other trait-like attributes (e.g., cognitive schemas) can moderate the relationship between stress and depression, thus predisposing some individuals to depression (Akiskal et al., 1983; Beck,

1983; Blatt, 1974). Support for such ideas comes from research linking depression and a variety of personality traits, including dependency, autonomy, self-criticism, neuroticism, introversion, and hopelessness (Beck et al. 1985; Blatt et al., 1982). A brief review of these personality traits is provided in the following sections.

3.3.1. Sociotropy vs. Autonomy / Dependency vs. Self-criticism

Beck (1983) has described two major constructs, autonomy and sociotropy, which are associated with depressive vulnerability. Individuals high in autonomy show exaggerated concerns with performance evaluation and place high value on personal independence, control, and achievement. Conversely, people high in sociotropy exhibit a strong need for approval, the desire to maintain attachments, and a vigilant avoidance of social rejection. According to the personality–life event congruence model, high levels of sociotropy, marked by the powerful desire for close relationships, can leave individuals vulnerable to depression in the event of an interpersonal loss. A high level of autonomy, on the other hand, can render individuals susceptible to depression when the needs for self-definition, self-control, and self-worth are negated.

Early work by Blatt (1974) delineated similar personality styles – dependent and self-critical - that have been linked to increased vulnerability to depression. Dependent individuals, like those high in sociotropy, have strong needs to be cared for and protected. Self-critical individuals, similar to those high in autonomy, are achievement-oriented, have high internal standards, and are continuously striving for perfection. In Blatt's model, dependent individuals are at increased risk for "anaclitic depression," which is a form of depression that usually develops in childhood, often following the loss of an attachment figure. Blatt argued that self-critical individuals, on the other hand, are prone

to “introjective depression”, a developmentally later form stemming from the internalization of criticism and derogation by others, particularly parents.

In addition, Blatt (1974) and Beck (1983) hypothesized that the two personality styles influence the organization of depressive symptoms. Blatt proposed that the primary features of dependent depression are feelings of helplessness and weakness, fear of abandonment, and the desire to be cared for. The primary experience of individuals suffering from self-critical depression, on the other hand, is one of guilt, inferiority, failure, and worthlessness.

Several studies (though not all; see Abramson et al., 2002 for a review), have reported findings in line with the sociotropy and autonomy dimensions and the personality–life event congruence model. Mazure and colleagues (2000), for example, found that rates of depression were three times higher in the presence of trait-like concern about disapproval or trait-like need for control. Further, in a study of late-onset depression, depressed status was predicted in similar fashion by the interaction between sociotropy and negative events and the interaction between between autonomy and negative events (Mazure et al., 2002). Extending these findings, a recent study by Morse et al. (2005) found that older adult patients in remission from depression who experienced life events that matched their personality experienced exacerbation of depressive symptoms over 6 months.

3.3.2. Neuroticism

Neuroticism is a stable and heritable personality trait that involves the experience of negative states manifested as anxiety, low mood, hostility, and emotional instability (Eysenck, 1990; Eysenck und Eysenck, 1985). Clark and Watson (1991) have described a similar construct, negative affectivity, which represents a propensity to experience a

broad range of negative mood states. Additionally, negative affectivity leads to negative cognitions, low self-esteem, and life dissatisfaction (Clark et al., 1994).

Neuroticism has received considerable attention from researchers interested in personality characteristics that might predict the frequency of stressful life events. Using a nonclinical sample, Poulton and Andrews (1992) found that high scores on neuroticism were good predictors of negative interpersonal life events. The authors speculated that individuals who are highly emotionally reactive behave in ways that generate stressful interpersonal events (Hammen, 2005).

Neuroticism appears to influence the risk for depressive illness in two distinct ways. First, neuroticism moderates the pathogenic effects of stress exposures. Kendler and coworkers (2004) reported this effect, demonstrating that neuroticism is an important moderator of the effects of stress on depression. Second, neuroticism predicts the frequency of stressful life events. Consistent with this view, neuroticism has indeed been found to predict the occurrence of stressful life events (Van Os and Jones, 1999), particularly those of an interpersonal nature (Kendler et al., 2003).

4. Methodological Issues in Stress Assessment

In a recent review article, Hammen (2005) summarized two major challenges that stress researchers have encountered over the years: (1) making certain that the stress is not confounded with the outcome variable (i.e., depression), and (2) ensuring that the stressfulness of an event can be understood in terms of the individual's construals. Life event checklists have been limited in both of these areas (Kessler 1997). Endorsement of

checklist items and their accompanying severity ratings can reflect interpretations and judgments that are influenced by the current emotional state of the person. Consequently, each item selected could have personal meanings that vary from person to person.

To address both issues, researchers have developed interview methods, which are generally regarded as the standards in the field. Brown and colleagues, for example, developed a method of assessing stressor severity in context; stressful event occurrences are identified systematically and the context of each event is then explored. This assessment method, called the Life Events and Difficulties Schedule (LEDS; Brown and Harris, 1989), draws out details about event timing and duration. This approach allows for the coding of both acute and chronic events, and the extent to which the events were dependent or independent of the individual's behavior. Research comparing the interview method versus checklist methods has generally been supportive of the former, finding that the interview approach leads to (1) better outcome prediction; (2) more accurate recall and precise dating of event occurrence; and (3) reports that are less biased by mood and current cognitive vulnerability (McQuaid et al., 2000; Kessler, 1997; Hammen, 2005).

5. Depression and Cognitive Vulnerability

The role of cognitive styles or vulnerabilities in the etiology and course of depression has received substantial empirical scrutiny (see Abramson et al., 2002 for a review). In general, cognitive vulnerabilities take the form of rigid and dysfunctional interpretations of the self and the world, and/or maladaptive attributional styles.

According to cognitive theories of depression, negatively-biased interpretations of stressful events increase an individual's likelihood of developing depression (Abramson et al., 1989; Beck, 1967). In the following section, a brief overview of two prominent cognitive theories of depression will be presented: Beck's cognitive theory of depression (Beck et al., 1979) and the Hopelessness Theory (Abramsom et al., 1989)

5 1. Beck's Cognitive Theory of Depression

Beck's cognitive theory of depression emphasizes that negative views of the self, the future, and the world, centered around themes of loss, inadequacy, failure, and worthlessness, constitute a substantial cognitive vulnerability to depression (Beck et al., 1979). These rigid and extreme beliefs often involve the views that one's worth stems from being perfect or gaining approval from others. According to Beck, negative events (e.g., stressors) can activate depressogenic self-schemata, which in turn lead to the activation of automatic negative thoughts about oneself, the world, and the future (the *negative cognitive triad)*. These automatic thoughts, in turn, lead to sadness and other depressive symptoms (**FIGURE 1**). Beck's model emphasizes the interaction of cognitive vulnerability and negative stress; in the absence of negative events, the depressogenic vews of the self remain latent and do not lead to negative automatic thoughts or depressive symptoms (Haaga et al., 1991)

At a later stage, Beck extended his theory by postulating that depression is especially likely to occur when there is a match (congruence) between the individual's personality styles or schemas and the occurrence of a stressor whose content is relevant to the personality style (Beck, 1983). As noted above, sociotropic individuals are more

likely to become depressed when they experience stressors characterized by social rejection or interpersonal losses. In contrast, individuals high in autonomy may be more vulnerable to depression when they experience stress linked to failures and loss of personal control. Along similar lines, Beck (1983) proposed that sociotropy and autonomy influence the organization of symptoms during depression (see also Blatt, 1974). Accordingly, during a depressive episode, a highly sociotropic individual will experience symptoms that are organized around the theme of interpersonal loss (i.e. feeling weak, lonely, abandoned). When a highly autonomous individual is depressed, the symptoms experienced will likely involve themes of defeat and withdrawal (i.e., guilt, worthlessness, social withdrawal).

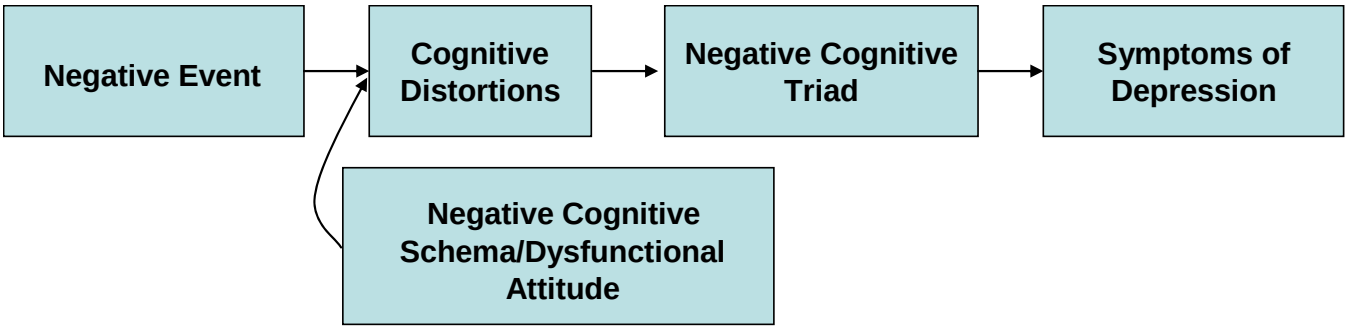

FIGURE 1: Casual chain in Beck's cognitive model of depression (adapted from Abramson et al. 2002).

Several prospective studies have provided empirical support for Beck's theory by showing that the combination of dysfunctional attitudes and negative events predicted increases in depressive symptoms over time (Brown et al., 1995; Dykman and Johll, 1998; Joiner et al., 1999; Klocek et al., 1997). However, studies testing the congruence

models reviewed above have yielded somewhat inconsistent findings (for a review see Coyne and Whifffen, 1995).

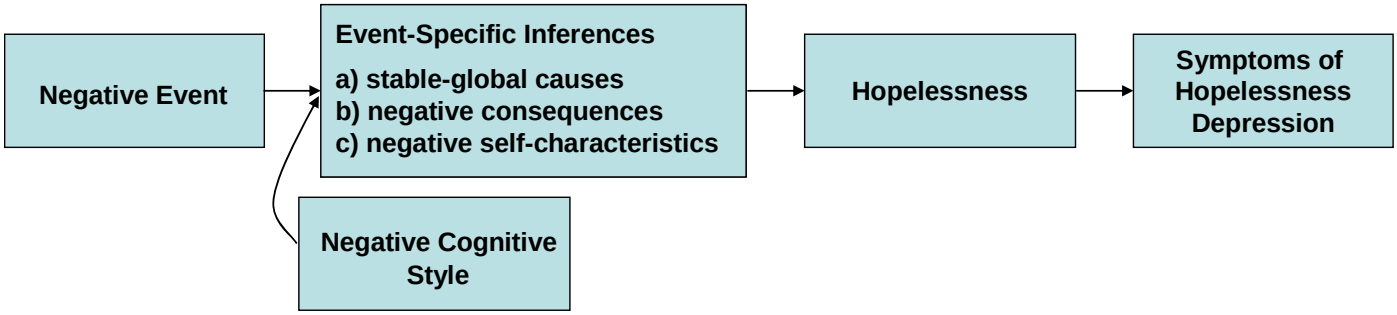

FIGURE 2: Casual chain in Abramson's Hopelessness theory of depression (adapted from Abramson et al. 2002).

5.2. Hopelessness Theory

The Hopelessness theory (Abramson et al., 1989) was derived from Seligman's theory of learned helplessness and depression (Seligman, 1972). Seligman's work led to the view that expectancies of no control in response to uncontrollable stressors could trigger depression. According to the Hopelessness theory, depression is most likely to occur when two conditions are met: (1) the individual expects that positive outcomes will not occur or that highly negative outcomes will occur; and (2) the individual feels powerless to change this situation (for a review, see Abramson et al., 2002). An important component of the hopelessness model is that cognitive processes (attributions and inferences about stressors) mediate the association between depression and negative events (**FIGURE 2**). Specifically, hopelessness, and in turn depression, are likely to occur when negative events are (1) attributed to stable and global causes (i.e., are likely to persist over time and affect various domains) and viewed as important; (2) perceived as

likely to initiate a cascade of other negative events; and (3) interpreted as a sign of personal worthlessness. As in Beck's theory, Abramson's model involves an interaction effect: individuals prone to make depressogenic inferences about negative events are only at increased risk for depression in the presence of negative life events.

Recent prospective studies have provided support for the hopelessness theory of depression. During a 2.5-year prospective follow-up, individuals who exhibited a negative cognitive style (1) showed a greater likelihood to develop MDD (Alloy et al., 2006), and (2) experienced more episodes of depression, more severe episodes, and more chronic courses (Iacoviello et al., 2006) compared to control subjects. Similarly, a number of other studies have found that the endorsement of negatively-biased cognitions is associated with an elevated risk for depressed mood and depressive symptoms in combination with negative life events (Alloy et al., 1997; Joiner et al., 1999; Lewinsohn et al., 2001; Reilly-Harrington et al., 1999). Finally, individuals whose depression had remitted exhibited more negative cognitive styles compared to never-depressed individuals. Such a finding raises the possibility that cognitive vulnerability might represent a trait marker for depression (Haffel et al., 2005).

6. Toward a synthesis: The Interaction between Depression, Stress, and Cognitive Vulnerability

As reviewed in Section 5, cognitive vulnerability-stress theories of depression suggest that depressogenic schemata or maladaptive attributional styles exist as cognitive diatheses in individuals at risk for depression, and these diatheses must then be activated by relevant stressors in order to exert more damaging effects on information processing

and mood (Beck et al., 1979; Abramson et al., 1989). Consistent with these theories, the effects of cognitive dysfunctions are particularly potent in interaction with environmental factors, in particular life stressors.

With respect to Beck's theory, Brown et al. (1995) showed, for example, that dysfunctional attitudes interacted with a naturally occurring stressor to prospectively predict depressive symptoms. Similarly, Flett et al. (1995) reported that the interaction between elevated DAS scores and stressful life events predicted depressive symptoms 3 months later. Similar findings were found in an outpatient sample (Hewitt et al., 1996). Further research by Dunkley et al. (2000; 2003) found that dysfunctional attitudes, specifically perfectionism, exerted an influence on both actual and perceived daily stress, which in turn predicted depressive symptomology. In Dunkley's studies, the *perception* of stress (as well as avoidant coping and low social support) emerged as an important mediator that accounted for the association between dysfunctional attitudes and depressive symptoms. The dysfunctional (perfectionistic) attitudes themselves are hypothesized to produce high levels of stress because these types of cognitions involve rigid evaluations of events, the magnification of negative aspects of events, and extreme concern about rejection and loss of respect. In a recent study using path analysis, Dunkley et al. (2006) found that DAS (perfectionism) scores predicted depressive symptoms in a 3-year follow-up with a clinical sample characterized by substantial PD comorbidity.

Similar findings have emerged from studies on constructs associated with the hopelessness theory of depression. In a non-clinical sample, Metalsky et al. (1993) found that the persistence of depressive symptoms was predicted by the interaction between depressogenic cognitive style and a naturalistic stressor (failure on an exam). Hankin et

al. (2005) found that both trait-like depressogenic cognitive style and negatively-biased thoughts about stressors predicted variation in daily depressive symptoms in a non-clinical sample. Specifically, negative thoughts about daily stressors accounted for nearly 30% of the association between depressogenic cognitive style and depressive symptoms. Finally, Safford and coworkers (in press) conducted a prospective study and found that, compared to control subjects, individuals with negative attitudes and cognitive patterns generated significantly more stressful life events. Importantly, the association was only significant for dependent interpersonal events. The absence of a link between depressogenic cognitive style and independent (fateful) or achievement-related events underscores the presence of a stress generation effect.

Overall, these findings suggest that maladaptive cognitions and dysfunctional attitudes do not operate in a vacuum, but interact powerfully with environmental stressors. Not only is a depressogenic cognitive style associated with negative inferences *in response* to negative life events, it also contributes to the generation of stressful events, particularly those with interpersonal components. Both cognitive style and the experience of stress are assumed, in turn, to increase vulnerability to depression.

II. PERSONALITY DISORDER

"In most of us, by the age of thirty, the character has set like plaster and will never soften again."

William James, Principles of Psychology, 1981

"We continue to shape our personality all our life."

Albert Camus

Each of us has a personality – a distinctive and lasting pattern of inner experience and outward behavior. Each of us tends to react in predictable and consistent ways. These consistencies, often called personality traits, emerge early in life via the transactions between inherited temperamental characteristics and enviromental influences. Yet for most of us, personality traits are also flexible. We learn from experience. Through interactions with our environment, we explore various responses to see which are more effective. This is a flexibility that people who suffer from personality disorders often lack.

In contrast to mood disorders, which can be episodic and can crop up at any age, personality disorders are, by definition, enduring, inflexible, and maladaptive constellations of traits and behaviors that are typically in place by adolescence or early adulthood. These longstanding maladaptive patterns are seen across most of the person's interactions with people and the environment, and they differ markedly from the experiences and behaviors typically expected of people. Finally, the maladaptive

behaviors and traits cause significant and persistent functional impairment or personal distress (APA, 2000).

The prevalence of personality disorders in the general population has been estimated to be approximately 6-9% (Corruble et al., 1996), although some epidemiologic studies have suggested that up to 15% of adults in the USA have at least one personality disorder (Grant et al., 2004). Not surprisingly, estimates of personality disorder prevalence are higher in clinical samples. For example, research indicates that 20-50% of patients hospitalized for MDD meet criteria for a personality disorder, and up to 50-85% of MDD outpatients exhibit personality pathology (Yen et al., 2006). There also appear to be differences between inpatient and outpatient samples with regard to the rates of specific personality disorders. The dramatic cluster personality disorders (especially borderline and histrionic) tend to be more common in inpatient samples (Black et al., 1988), while outpatient samples tend to have higher rates of anxious-fearful-cluster personality disorders (Pilkonis and Frank, 1988).

1. Categorical and Dimensional Approaches to Personality Disorder

One of the most challenging issues facing the field of psychopathology is how to conceptualize personality disorders. Two general models have been proposed in the literature for classifying and explaining this group of disorders, one categorical and the other dimensional. There are substantial differences between these models with regard to form, assumptions about key constructs, and approaches to measurement (Livesley and Jackson, 1991, 1992; Trull and Durrett, 2005). A synopsis of these two models of personality disorders is presented in the following sections.

1.1. Categorical Approach

In the categorical model, currently employed by the DSM, the extent to which the disorder is present is represented dichotomously: disorder is either present, or it is not. In the DSM, each of the personality disorders is defined by a specific set of criteria, and positive diagnosis requires that the patient (1) exhibits an established number of the criteria by early adulthood, (2) displays the pathological behaviors and traits across a wide range of situations, and (3) experiences considerable impairment or distress. An individual who does not exhibit the minimum number of symptoms is technically viewed as being free of the disorder. The validity of these categorical constructs has been disputed, and many have advocated for a dimensional approach that recognizes both the continuous nature of the personality traits involved, and the likelihood that a smaller group of basic personality dimensions form the foundation of these disorders (Trull and Durrett, 2005; Widiger and Clark, 2000).

In its current form, the DSM (APA, 2000) organizes ten personality disorders into three clusters: odd or eccentric (Cluster A), dramatic, emotional, or erratic (Cluster B), and anxious or fearful (Cluster C). Cluster A includes paranoid, schizoid, and schizotypal personality disorders. Cluster B contains histronic, narcissistic, borderline and antisocial personality disorders. Finally, Cluster C includes avoidant, dependent, and obsessive-compulsive personality disorders. The creation and acceptance of these three clusters suggests an already-present alternative to viewing each of the personality disorders as distinct and mutually exclusive entities. A brief overview of the cardinal features of each cluster is presented below.

1.1.1. Cluster A

Patients with Cluster A disorders - paranoid, schizoid and schizotypal - exhibit discomfort in interpersonal situations, are emotionally distant and difficult to engage, and tend to isolate themselves from others. They typically display odd or eccentric behaviors that resemble those seen in schizophrenia, such as suspiciousness, social withdrawal, and unusual ways of thinking and perceiving things (APA, 2000). However the symptoms in Cluster A are not as extreme or impairing as those seen in schizophrenia.

Individuals with *paranoid personality disorder* hold a deep-rooted distrust of other people. Such individuals avoid close relationships out of the belief that other people intend them harm. People with *schizotypal personality disorder* are uncomfortable in close relationships and come across as odd in their behavior, speech, and appearance. Further, the disorder is characterized by unusual beliefs and perceptual experiences (e.g., magical thinking, ideas of reference). Schizotypal individuals are socially isolated and highly suspicious of others. Finally, people with *schizoid personality disorder* also avoid social relationships, though the motivation for these individuals is a genuine desire to be alone. Schizoid personality disorder is also characterized by a profoundly flattened affect and an indifference to both the positive and negative responses of others.

Collectively, this cluster is often referred to as the "schizophrenic spectrum cluster" because of similarities to schizophrenia symptomology. Supporting this view, Cluster A pathology, particularly schizotypal personality disorder, is more prevalent than average among first-degree relatives of people with schizophrenia (Raine, 2006).

1.1.2. Cluster B

The behaviors of individuals with Cluster B personality disorders - antisocial, borderline, histrionic, and narcissistic - are so dramatic, emotional, or erratic that it is almost impossible for them to have relationships that are truly reciprocal and rewarding. These patients engage in behavior that is excessively demanding, manipulative, and inappropriate, and their lives are marked by tremendous emotional instablility or impulsivity. Characteristically, people with *antisocial personality disorder* behave in persistently deceitful and reckless ways. Antisocial individuals have little regard for the rights of others, lack remorse, and often engage in impulsive and aggressive behavior. Individuals meeting criteria for *borderline personality disorder* have extreme difficulty with emotion regulation, which leads to quick and dramatic shifts in mood. Accompanying the emotional volatility are an unstable self-image and problems with impulsivity, all of which lead to significant instability in relationships. Finally, *histrionic personality disorder* is characterized by overly dramatic and attention-seeking behavior. Histrionic individuals are self-centered, overly focused on physical appearance, and rather superficial despite their grand emotional displays.

1.1.3. Cluster C

People with Cluster C disorders - avoidant, dependent, and obsessive-compulsive - engage in behavior driven by anxiety and fear. These patients experience ideas and sensations that cause distress and interfere with functioning. Although there appears to be a great deal of overlap between Cluster C disorders and Axis I anxiety and

depressive disorders, researchers have not found direct links between them (Comer, 2007).

Subjects with *avoidant personality disorder* view themselves as unappealing or inferior to others and avoid social situations unless they are sure others will like them. The avoidance of interpersonal contact is driven by overwhelming feelings of inadequacy and extreme fear of being negatively evaluated or rejected. *People with dependent personality disorder*, on the other hand, are clingy and submissive. There is an excessive desire for guidance and reassurance, a fear of separation, and a need to be taken care of. Finally, individuals with *obsessive-compulsive personality disorder* are highly concerned with control, neatness, and perfection. This pervasive focus on order often results in a loss of flexibility, openness, and efficiency that can be frustrating to coworkers, family, and friends.

1.2. Dimensional Model

Several problems have been identified with the current categorical conceptualization of personality disorders. These issues include arbitrary diagnostic thresholds, the potential for lost clinical information due to the all-or nothing categorization of patients, considerable heterogeneity within specific personality disorders, and extensive similarty between many of the disorders. Further, the blurry boundaries between disordered and normal personality organization present problems for the categorical paradigm. Most problematic, however, is the fact that the symptoms of many DSM-based personality disorders overlap so extensively that it can be difficult to distinguish one from another (Gunderson and Ronningstam, 2001). In clinical settings

these problems lead to misdiagnosis, compromised validity of the diagnostic categories, and poor reliability.

To resolve these problems, critics have suggested that an alternative, dimensional approach should be used for conceptualizing and diagnosing personality disorders (Shedler and Westen, 2004; Trull and Durrett, 2005; Widiger and Clark, 2000). In this approach, disorders would be organized by the acuteness of key traits, or personality dimensions, rather than by the presence or absence of the specific criteria currently listed in the DSM. In this framework, each key trait (e.g., neuroticism) is represented by a continuum on which there is no clear boundary between normal and abnormal. Personality disorders are, in this model, conceptualized as extreme values on multiple key traits.

Although a review of the dimensional models of personality and its disorders is beyond the scope of the present work, it is important to note that a large body of research indicates that the basic structure of personality might consist of five "supertraits" or factors: *neuroticism* (the tendency to experience negative emotions), *extroversion* (the tendency to experience positive emotion and seek out interpersonal experiences), *openness to experience* (the pursuit and appreciation of new experiences), *agreeableness* (the tendency toward altruism over antagonism), and *conscientiousness* (the motivation to pursue goals in an organized and meticulous fashion) (Costa and McCrae, 2005). Research indicates that the majority of personality disorders involve high levels of neuroticism and low levels of agreeableness. In addition, low extraversion is central to the disorders that involve reclusiveness (schizoid, schizotypal, and avoidant). As another example, people with obsessive-compulsive personality disorder tend to display extreme

levels of conscientiousness, whereas those disorders characterized by impulsivity (antisocial and borderline) involve low levels of conscientiousness.

2. Personality Disorder and Depression Comorbidity: Treatment Implications

As mentioned in Section I, studies indicate that a substantial proportion of depressed patients have comorbid personality disorders (20-50% of inpatients and 50-85% of outpatients; Brieger et al., 2003; Yen et al., 2006). Evidence from a number of studies suggests that MDD-PD comorbidity predicts poorer outcomes with regard to both the course and treatment of depression. Studies on the response of depressed patients to tricyclic antidepressants, for example, have found that that co-occurring neurotic, hypochondriacal, and hysterical personality traits predicted a poor response to these medications (Bielski and Friedel, 1976). Similarly, Weissman and colleagues (1978) found that the strongest predictor of treatment outcome (after psychotherapy or drug therapy) was level of neuroticism. In a review of several studies in this area, Shea et al. (1992) concluded that depressed patients with comorbid personality disorders had poorer outcomes with drug therapy compared to patients without personality disorders.

More recent studies have linked MDD-PD comorbidity to: longer latency to both positive treatment response (Pilkonis and Frank, 1988) and recovery (Meyers et al., 2002); greater likelihood of relapse (Hart et al., 2001; Ilardi et al., 1997); shorter time to relapse (Cyranowski et al., 2004); persistence of depressive symptoms (Pepper et al., 1995; Riso et al., 1996); fewer improvements in functioning after psychological treatments (Shea et al., 1990); and poorer response to antidepressant medication, short-term psychotherapy, and electroconvulsive therapy (Peselow et al., 1992; Sato et al.,

1993; Thompson et al., 1988; Sareen et al., 2000). The importance of considering the influence of psychosocial factors in combination with personality variables was underscored by Ezquiaga et al. (1998), who found that the combination of a comorbid personality disorder, a history of depression, low Global Assessment of Functioning, and poor social support most strongly predicted incomplete recovery from MDD. A recent meta-analysis has also established that, compared to depression alone, depression with a comorbid personality disorder is associated with twice the risk for a poor outcome, irrespective of treatment modality (drugs, psychotherapy, or combined treatment) (Newton-Howes et al., 2006).

In spite of these significant findings, it is important to note that several studies have failed to find a link between MDD-PD comorbidity and poor treatment response (e.g. Fava et al., 1994, 1997, 2002; Mulder et al., 2003; see Kool et al., 2005 for a review). Several phenomena might account for the inconsistencies in this literature. First, the varying influences of individual personality disorders might explain the different outcomes (Fava et al., 1997). Consistent with this hypothesis, Sato et al (1994) found that only comorbid personality disorders from Cluster A had a negative effect on outcome in a study of patients treated with antidepressants. Similarly, Skodol et al. (2005) recently reported that subjects with comorbid MDD-schizotypal and MDD-borderline experienced more functional impairment than MDD subjects with comorbid obsessive-compulsive personality disorder.

A second explanation for the inconsistencies in the literature is that specific personality disorders might differentially influence MDD outcomes through unique associations with factors that increase the overall risk of depression. Such factors might

include negative attributional biases and maladaptive cognitive patterns. In this framework it is important to recall that personality disorders are characterized by deeply ingrained and rigid patterns of perceiving, thinking, relating to others (DSM-IV, APA, 2000). Indeed, studies have linked Axis II symptomology to dysfunctional attitudes and maladaptive cognitive patterns, even in samples of formerly depressed (Ilardi and Craighead, 1999) and never-depressed subjects (O'Leary et al., 1991). Intriguingly, in a recent study of postpartum depression, maladaptive cognitive patterns mediated the link between personality pathology and depressive symptoms (Church et al., 2005).

The studies presented in **Section III** were designed to test the potential contributions of stress appraisal and cognitive vulnerability, as well as their interaction, on treatment outcome in a large sample of MDD outpatients treated with a standard antidepressant. Relevant literature emphasizing a link between personality pathology and (1) elevated stress responsiveness; and (2) maladaptive cognitive patterns will be reviewed in Section III.

3. Personality Disorder and Depression Comorbidity: Etiological Models

In Section II, evidence was summarized highlighting substantial co-occurrence of depression and personality disorders. In the following sections, four etiological models of comorbidity will be briefly presented. In general terms, these models can be divided in two categories (for reviews see Clark, 2005; Mineka et al., 1998): those postulating a temporal relationship between the two conditions (the vulnerability and pathoplasty models), and those positing that the two forms of psychopathology stem from the same

etiological processes (the shared factor and spectrum models). The first category assumes a temporal (i.e., causal) relation between the two types of disorder, while the latter category does not.

The predisposition or vulnerability model. The main hypothesis in this model is that a prior disorder increases the likelihood of later psychopathology. Accordingly, certain temperamental and personality factors (or disorders) increase the risk of developing new forms of psychopathology. A high level of neuroticism, for example, may be a risk factor for depression (Kendler et al., 2006). By assuming that the first condition puts an individual at risk for the second, the predisposition model explicitly advances a causal connection between disorders.

The pathoplasty model. This model postulates that the severity, course, and outcome of a later disorder can be moderated by the experience of a prior disorder. As in the vulnerability model, the pathoplasty model describes a temporal relation between two conditions. Two variants of the pathoplasty model have been articulated, the scar and complication models, and both are particularly applicable to MDD-PD comorbidity (Clark, 2005). Both variants posit that experiencing psychopathology leads to changes in personality (Levinsohn et al., 1981). In the *scar model*, such changes are severe and enduring . After a major depressive episode, for instance, an individual's trait neuroticism might remain above premorbid baseline levels. The *complication model*, on the other hand, predicts that the individual's neuroticism would revert to baseline levels. In line with the state-dependent hypothesis of the complication model, Ouimette et al. (1996) demonstrated that currently depressed subjects differed from formerly depressed subjects

on measures of several personality traits (autonomy, dependency, self-criticism, neuroticism, extraversion, and psychoticism).

Common/shared cause or liability model. This model hypothesizes that comorbid disorders share a common genetic diathesis. Recent support for this model was provided by Kendler and coworkers (2006), who investigated the relationship between MDD and personality pathology in a twin study involving 20,692 same-sex twin pairs. In this study, neuroticism was a strong predictor of both lifetime and new-onset MDD. Importantly, the link between neuroticism and MDD was accounted for, in large part, by shared genetic risk factors.

The spectrum model. This model postulates underlying continua that extend from normal functioning to mild, moderate, and severe psychopathology. The spectrum view provides an explanation for the overlap and comorbidity of mental disorders: one disorder (e.g., schizophrenia) is viewed as a more severe form of the another (e.g., schizotypal personality disorder).

4. Personality Style and Personality Disorder

4.1. Sociotropy vs. Autonomy /Dependency vs. Self-Criticism

Several studies have shown that sociotropic/dependent and autonomous/self-critical personality styles are significantly related to Axis II psychopathology (Ouimette et al., 1994). For example. Ouimette et al. found significant relationships between autonomy/self-criticism and schizoid and schizotypal traits. Avoidant personality disorder, on the other hand, was related to all four personality styles. These findings

suggest that both schizoid/schizotypal and avoidant individuals maintain distance from others, but that avoidants are differentiated by their desire for intimacy and their potential for dependency in the few close relationships that they do establish. Pilkonis and Frank (1988) have reported similar findings, noting that elevated autonomy is a feature of obsessive-compulsive, schizoid and antisocial personality disorders, while dependency is a central aspect of dependent and borderline personality disorders.

4.2. Neuroticism

According to current conceptualizations, most personality disorders are characterized by extreme levels of neuroticism (Skodol et al., 2005; Kendler et al., 2003). In addition, research has established positive associations between neuroticism and interpersonal sensitivity, need for approval, and social inhibition (Miller and Pilkonis, 2006). Interestingly, individuals high in neuroticism perceive themselves as possessing a wide array of interpersonal problems, while significant others (e.g., partners, family members, friends) report that these individuals overestimate their interpersonal shortcomings. Such a finding corresponds well with research showing that neuroticism predicts the frequency of stressful life events (Kendler et al., 2003; Magnus et al., 1993), quality of social support (Windle, 1992), as well as interpersonal conflict, job loss, and financial difficulties (Bolger and Schilling, 1991; Kendler et al., 2003).

5. Personality Disorder, Stress and Depression

Theoretical arguments postulate that certain personality factors predict exposure to stressful life events, reactivity to those events, or both. Further, these associations can account, in part, for the relationship between personality and various forms of psychopathology (Bolger and Zuckerman, 2005). In this framework it is also assumed that specific coping strategies can influence the development of personality-based differences in stress reactivity. In an important test of these hypothesized links, Daley et al. (1998) evaluated two models of the relationship between personality disorder symptomology and depression by including life stress as an intervening variable. In the first model, which evaluated potential mediating effects, life stress was assumed to explain the link between personality pathology and subsequent depression. In this view, an individual with a personality disorder elicits stressful life circumstances or interpersonal distress, which in turn predict the onset of depression. In the second model, which evaluated possible moderating effects of life stress, personality disorders were seen as vulnerability factors when coupled with stress. This model emphasized reactions to stressful events, and posited the following: (1) individuals with personality disorders have fewer psychological and social resources than people without such disorders, (2) as a result, they will be more vulnerable to stressors, and (3) accordingly, they will be more likely to respond to stress with depressive symptomatology. Findings provided clear support for the mediation model. Personality disorder symptoms, specifically Cluster A and B symptomatology, contributed to the generation of dependent life stressors over a 2-year period, which in turn predicted later depressive symptoms (Daley et al., 1998).

III. EMPIRICAL STUDIES INVESTIGATING THE ROLE OF PERSONALITY VULNERALIBILITY, COGNITIVE VULNERABILITY, AND STRESS APPRAISAL ON TREATMENT OUTCOME IN MAJOR DEPRESSION

Personality Disorders and Perceived Stress in Major Depressive Disorder

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Abstract

Background. In recent years, the investigation of comorbidity between major depressive disorder (MDD) and personality disorders (PDs) has attracted considerable interest. Whereas some studies have reported that the presence of PDs has adverse effects on the course and treatment of MDD, others have failed to demonstrate this link. This inconsistent pattern of findings invites the possibility that specific PD comorbidity might affect the course of MDD by modulating factors that increase the overall risk of depression, including an elevated tendency to perceive stress (stress appraisal).

Methods. To investigate whether the presence of a specific PD cluster (cluster A, B, or C) was associated with elevated levels of stress appraisal, we administered the Perceived Stress Scale (PSS) before and after treatment to 227 MDD outpatients enrolled in an 8-week open-label treatment with fluoxetine.

Results. Following antidepressant treatment, multiple linear regression analyses revealed that the presence of Cluster A, but not Cluster B or C, was associated with higher levels of perceived stress, even after adjusting for differences in baseline depression severity and PSS scores, as well as various sociodemographic variables (gender, age, education, employment status, marital status).

Conclusions. The presence of Cluster A PD comorbidity was uniquely associated with elevated stress appraisal after antidepressant treatment, raising the possibility that stress exacerbation might be an important factor linked to poor treatment outcome in MDD subjects with Cluster A pathology. Longitudinal studies directly testing whether Cluster A pathology might predispose MDD subjects to experience more life stressors and/or react more poorly to them are warranted.

Introduction

Over the years, increasing attention has been devoted to investigating the comorbidity between major depressive disorder (MDD) and personality disorders (PDs). In general, the presence of PDs is assumed to have adverse effects on the course and treatment of MDD. Consistent with this hypothesis, co-occurrence of MDD and PD has been associated with poorer response to treatment in most (Reich and Green, 1991; Peselow et al., 1992; Sato et al., 1993) but not all (Fava et al., 1994, 1997) studies, and with higher risk of depressive recurrence (Ilardi et al., 1997; Hart et al., 2001). Moreover, compared to MDD subjects without PD, those with comorbid PD reported significantly greater impairments in social and emotional functioning and lower well-being (Skodol et al., 2005); higher levels of residual symptoms (Shea et al., 1990); slower recovery (Patience et al., 1995); higher levels of psychotropic utilization at a 1-year follow-up (Casey et al., 2004); and more frequent referral to psychiatric services (Moran et al., 2001).

On the other hand, others have failed to find a link between comorbid PD and poor treatment response (Fava et al., 1994, 1997, 2002; Russell et al., 2003; Mulder et al., 2003). Echoing these negative findings, a recent meta-analysis including findings from six randomized controlled trials with strict methodological criteria found that MDD subjects with comorbid PD had only a 3% lower remission rate compared to MDD subjects without PD, a difference that was not statistically significant (Kool et al., 2005). Taken together, these findings raise the possibility that comorbid personality pathology is

not necessarily associated with poor treatment response, and that other intervening variables might be involved.

One possibility is that the three PD clusters based on the Diagnostic and Statistical Manual (DSM; American Psychiatric Association, 1987, 2000), Cluster A (paranoid, schizoid, schizotypal), Cluster B (borderline, histrionic, narcissistic, antisocial), and Cluster C (avoidant, dependent, obsessive-compulsive) may be differentially related to the course and outcome of depression. Sato et al. (1994), for example, found that only the presence of a Cluster A PD had a significant negative effect on short-term outcome in depression, while Fava et al. (1994) showed that the presence of Cluster B (but not Cluster A or C) PD in MDD was associated with a more favorable outcome following treatment with fluoxetine. Similarly, in a cohort of depressed patients undergoing a 6-month treatment, the presence of symptoms of avoidant, schizotypal, and schizoid, but no other, PD was associated with poorer outcome (Mulder et al., 2006).

A second, not mutually exclusive, possibility is that the presence of comorbid PD among MDD subjects is associated with higher occurrence of factors that increase the risk of depression, such as life stressors and poor social support (Pfohl et al., 1984). Consistent with this hypothesis, in a community sample, symptoms of Cluster A and B, but not Cluster C, disorders predicted interpersonal chronic stress and self-generated episodic stress over 2 years, which in turn increased the vulnerability for depressive symptoms (Daley et al., 1998). Thus, in the Daley et al.'s study, life stress mediated the relationship between personality pathology and later depression, even when controlling for initial depressive severity.

Findings of a possible mediating role of stress on the relationships between PD and depression are intriguing, particularly since stress has been implicated in the etiology and maintenance of depression (Kendler et al., 1999; Brown and Harris, 1989; Hammen, 2005; van Praag, 2004), and has been associated with poorer treatment outcome and more frequent relapse (Tennant, 2002). Of note, research has suggested that risk for depression increases when individuals perceive stress as uncontrollable, unpredictable, and severe, and deem coping resources as insufficient (Akiskal and McKinney, 1973; Cohen and Williamson, 1988; Hammen, 2005; Lazarus and Folkman, 1984). In addition, compared to pre-treatment levels, perceived stress markedly diminishes following antidepressant treatment, and the degree of stress reduction tends to be highly related to the degree of depressive symptom reduction (Fava et al., 1992).

In the present study, we evaluated 384 MDD outpatients enrolled in an 8-week open-label treatment with fluoxetine for the presence of Cluster A, B, or C PD, as defined by the DSM-III-R (American Psychiatric Association, 1987). To investigate whether PD was associated with elevated stress perception, a subgroup of these participants (n=227) filled out before and after treatment the Perceived Stress Scale (PSS; Cohen et al., 1983), which assessed the degree to which participants appraised their daily life as unpredictable, uncontrollable, and overwhelming. Specifically, our goal was to test whether the presence of a given DSM-III-R-based PD cluster predicted levels of stress after 8-week antidepressant treatment with fluoxetine. We hypothesized that the presence of Cluster A or Cluster B PD comorbidity would predict elevated levels of perceived stress in MDD outpatients.

Methods

Participants

Data from the current study were derived from a larger study conducted at the Depression Clinical and Research Program (DCRP) at Massachusetts General Hospital (Fava et al., 2002; Farabaugh et al., 2002). The main goal of the parent study, which included 384 outpatients between the ages of 18 and 65, was to evaluate the efficacy of fluoxetine in the treatment of MDD. In order to be enrolled in an 8-week open treatment of fluoxetine 20 mg/day, subjects were required to meet criteria for MDD, as assessed with the Structured Clinical Interview for DSM-III-R, Patient Edition (SCID-P; Spitzer et al., 1989), and have a score of ≥ 16 in the 17-item Hamilton Rating Scale for Depression (HAMD-17; Hamilton, 1960) at baseline (pre-treatment). Exclusion criteria included: pregnancy, breast-feeding, use of birth control, suicide risk, history of neurological illness, serious unstable medical illness, organic mental disorders, substance abuse during the last year, schizophrenia, delusional disorder, bipolar disorder, severe antisocial personality disorder, and mood-congruent or -incongruent psychotic features. History of multiple adverse drug reactions, allergy to the study drug, current use of other psychotropic drugs, and evidence of hypothyroidism also led to exclusion. Finally, subjects were excluded if they had previously shown non-response or intolerance to fluoxetine (60-80 mg/day) or if they had failed at least one adequate antidepressant treatment during their current major depressive episode (for more detail about inclusion/exclusion criteria, see Fava et al., 2002).

During the acute treatment, outpatients were seen biweekly for safety and efficacy assessments. At both baseline as well as at the end of the 8-week treatment, subjects were also administered the SCID-II (including its screening questionnaire) (First et al., 1997) to assess the presence of any personality disorder. All the clinical assessments (SCID-I, SCID-II, HAMD-17) were carried out by psychiatrists and clinicians at the DCRP, who were fully trained in their administration. Before entering the study, participants provided written informed consent to a protocol approved by the Institutional Review Board of the Massachusetts General Hospital.

Questionnaires

The Perceived Stress Scale (PSS; Cohen et al., 1983) was used to assess the degree to which participants appraised their daily life as unpredictable, uncontrollable, and overwhelming. The PSS was selected because it has been found to better predict stress-related psychological symptoms, physical symptoms, and health service utilization compared to commonly used life event scales (e.g., Cohen et al., 1983). This stress appraisal scale includes 14 items (e.g., "In the last week, how often have you felt that you were unable to control the important things in your life?"); each item is scored on a 5-point scale, ranging from 0 (never) to 4 (very often). The internal and short-term reliability (coefficient alpha reliability: 0.84; two-day test-retest reliability: 0.85; Cohen et al., 1983) have been found to be satisfactory. In the present sample, PSS scores at both the pre- and post-treatment assessment were available for 227 MDD subjects. With the exception of higher education ($t(382)=2.67$, $p<0.008$), these subjects did not differ in any

demographic or clinical variable compared to subjects without PSS data at both assessments.

Statistics

To evaluate the effects of the 8-week open fluoxetine treatment on depression severity and stress perception, two-tailed paired t-tests comparing pre- and post-treatment HAMD-17 (n=384) and pre- and post-treatment PSS scores (n=227), respectively, were performed in a first step.

Next, the effects of PD comorbidity on depression severity and stress perception were evaluated. Prior studies reported that a substantial proportion of MDD subjects no longer met DSM diagnosis of PD after antidepressant treatment (e.g., Joffe and Regan, 1988; Fava et al., 1994, 2002), raising the possibility that diagnosing PD in patients with active Axis I pathology may be confounded by the patient's state (Zimmerman, 1994). To avoid this issue, only MDD subjects meeting DSM-III-R criteria for Cluster A, B or C at both the pre- and post-treatment assessment were considered (hereafter, "stable PD"). These subjects were compared to MDD subjects who did not meet any PD criteria at either assessment. For both the pre- and post-treatment assessments, unpaired t-tests were used to compare the PSS and HAMD-17 scores of MDD subjects with a stable PD vs. those without any PD. A Bonferroni correction was applied to correct for the number of t-tests performed (3 clusters x 2 scales x 2 assessments = 12; $p = 0.05/12 = 0.0042$).

Subsequently, for each DSM-III-R PD cluster separately, a multiple linear regression was performed to assess the relationship between presence/absence of a given PD cluster and post-treatment PSS score adjusting for pre-treatment depression severity (HAMD-17)

and PSS scores as well as for various sociodemographic variables that have been previously found to affect PSS scores (Cohen and Williamson, 1988). All subjects with SCID-II and PSS data at both the pre- and post-treatment assessments were considered for these analyses. The post-treatment PSS score was the dependent variable and PD, the sociodemographic variables, and the baseline severity measures were the independent variables. The sociodemographic variables included age, gender, education (college degree, less than college degree), employment status (currently employed, unemployed), and marital status (currently married, not married). When considering Cluster A PD, 135 subjects (42 with stable Cluster A, 93 without any PD) were included in the regression analysis. For Cluster B, 133 subjects were evaluated (40 with stable Cluster B PD, 93 without any PD). Finally, for Cluster C, 213 subjects were considered (120 with stable Cluster C PD, 93 without any PD).

Results

Three hundred eighty-four subjects were enrolled in the 8-week open treatment of fluoxetine 20 mg/day (Fava et al., 2002). In this sample, 54.7% of the subjects were female (n = 210), 33.6% were married (n = 129), 56.5% completed at least a college degree (n = 217), and 62.5% were currently employed (n = 240). The mean age of this sample was 39.8 (S.D.: 10.5), and the mean baseline HAMD-17 score was 19.7 (S.D.: 3.5). The mean age of onset of the first MDD and the mean duration of the current MDD episode were 25.7 (S.D.: 12.9) and 3.3 years (S.D.: 5.9), respectively. Among the 384 subjects, 378 were administered the SCID-II at baseline; 243 (64.3%) met criteria for at least one PD before treatment. Among these 243 subjects, 87 (35.8%) had one comorbid

PD, 61 (25.1%) had two comorbid PDs, and 95 (39.1%) had three or more comorbid PDs (Fava et al., 2002). When considering the DSM-based PD clusters, 42 (17.3%), 40 (16.5%), and 120 (49.4%) met criteria for Cluster A, Cluster B, and Cluster C, respectively, at both the pre- and post-treatment assessment. Ninety-three subjects did not meet criteria for any PD at either assessment.

Following treatment with fluoxetine, there was a significant reduction in depressive symptoms, as measured by the HAMD-17 (paired t-test: 19.72±3.47 vs. 10.63±7.17; $t(382)=-26.09$, $p<0.0001$), and in levels of perceived stress, as measured by the PSS (paired t-test: 37.06±6.83 vs. 25.90±9.22; $t(226)=-17.50$, $p<0.0001$).

Cluster A

Out of the 42 MDD subjects with a stable Cluster A PD, 29 (69.1%) were males compared to 33 of the 93 MDD subjects (35.5%) who did not meet criteria for any PD ($\chi(1) = 13.13$, $p<0.005$). Eight of the 42 subjects (19.1%) with stable Cluster A, and 34 of the 93 (36.6%) of those never meeting criteria for any PD ($\chi(1) = 4.14$, $p<0.05$) were currently married. Subjects with stable Cluster A and those without any PD comorbidity did not differ with respect to education ($\chi(1) = 0.38$, ns), employment status ($\chi(1) = 0.14$, ns), or age (40.29±12.00 vs. 40.63 9.84; $t(133) = 0.18$, ns).

Compared to MDD subjects without any PD comorbidity, those with stable Cluster A PD had significantly higher post-treatment PSS and HAMD-17 scores as well as higher pre-treatment HAMD-17 scores (Table 1). After Bonferroni correction, only the group difference in post-treatment PSS score remained. The multiple regression analysis indicated that the presence of stable Cluster A PD significantly predicted elevated post-

treatment PSS scores even after adjusting for age, gender, education, employment status, marital status, pre-treatment PSS scores, and pre-treatment HAMD-17 scores (adjusted R^2 = 0.18; t = 2.05, p<0.05). Pre-treatment PSS score was the only other variable predicting post-treatment PSS scores (t = 2.59, p<0.015).

Cluster B

As for Cluster A, proportionally more males were represented in the MDD sample with Cluster B comorbidity (25/40 or 62.5% vs. 33/93 or 35.5%, $\chi(1) = 8.30$, p<0.005). Subjects with Cluster B comorbidity versus those without any PD did not differ with respect to education ($\chi(1) = 0.01$, ns), employment status ($\chi(1) = 0.31$, ns), or marital status ($\chi(1) = 1.03$, ns). MDD subjects with Cluster B comorbidity were significantly younger than those without any PD (36.13±10.62 vs. 40.63±9.84, t(131) = -2.37, p<0.02).

Compared to MDD subjects without any PD, those with stable Cluster B PD had significantly higher pre- and post-treatment PSS scores as well as higher pre-treatment HAMD-17 scores (p<0.05, corrected; Table 1). Contrary to the findings for Cluster A, the regression analysis indicated that the presence of a stable Cluster B PD was not a significant predictor of post-treatment PSS scores when adjusting for age, gender, education, employment status, marital status, pre-treatment PSS score, and HAMD-17 scores (adjusted R^2 = 0.09, t = 0.65, p > 0.51).

Cluster C

Subjects with stable Cluster C PD comorbidity did not differ from those without any PD with respect to education ($\chi(1) = 0.01$, ns), employment status ($\chi(1) = 1.56$, ns), marital status ($\chi(1) = 0.13$, ns), or age (39.97±10.80 vs. 40.63±9.84; t = -0.47, ns). As for the other clusters, more males were represented in the MDD sample with Cluster C comorbidity (62/120 or 51.7% vs. 33/93 or 35.5%; $\chi(1) = 5.55$, $p<0.05$).

Compared to MDD outpatients without PD, those with Cluster C PD had higher pre- and post-treatment PSS scores and HAMD-17 scores. When applying a Bonferroni correction, groups differed only in their pre-treatment HAMD-17 scores and post-treatment PSS scores ($p<0.05$ corrected; Table 1). As for Cluster B, the regression analysis indicated that the presence of stable Cluster C PD failed to predict post-treatment PSS scores when adjusting for age, gender, education, employment status, marital status, pre-treatment PSS score, and HAMD-17 scores (adjusted $R^2 = 0.12$, t = 1.33, p > 0.18).

Discussion

Stress and major life events have been implicated in the etiology and maintenance of depression (Kendler et al., 1999; Brown and Harris, 1989; Hammen, 2005; van Praag, 2004). Consistent with this hypothesis, prior studies have found that higher daily life stressors and perceived stress were associated with poorer outcome in major depressive disorder (Tennant, 2002). The main goal of this study was to investigate whether the presence of a stable PD comorbidity, specifically a DSM-III-R-based Cluster A, B or C PD, predicted the degree of perceived stress following an 8-week open-label treatment

with fluoxetine in MDD outpatients. Based on prior findings in the literature (e.g., Daley et al., 1998; Sato et al., 1994), we hypothesized that the presence of enduring Cluster A or Cluster B PD comorbidity would be associated with elevated levels of pre- and post-treatment perceived stress.

Compared to MDD outpatients without any PD, those with a stable PD generally showed elevated levels of stress appraisal and depression severity both before and after the treatment. When appropriate statistical corrections were applied, MDD subjects with stable Cluster A, B, or C PD reported significantly higher PSS scores after antidepressant treatment. In addition, stable Cluster B comorbidity was associated with significantly elevated depression severity and stress perception before the treatment as well, whereas MDD outpatients with stable Cluster C comorbidity were also significantly more depressed before the treatment compared to MDD subjects without any PD. Interestingly, in the regression analyses, only the presence of a Cluster A PD predicted post-treatment PSS scores after controlling for initial depression severity and PSS scores as well as various demographic variables (age, gender, education, employment status, marital status). Accordingly, the enduring presence of Cluster A comorbidity explained unique variance in stress appraisal after antidepressant treatment, above and beyond initial depression severity and perceived stress, confirming our a priori hypothesis. For Cluster B, the expected relationship did not emerge after the proper adjustments.

The present finding highlighting a specific link between stable Cluster A comorbidity and elevated stress appraisal post-treatment is intriguing. Various factors might explain this link. First, in both community (Camisa et al., 2005; Coolidge et al., 1994; Dyce and O'Connor, 1998; Costa and McCrae, 1990) and clinical (Blais, 1997;

Gurrera et al., 2005; Morey et al., 2000) samples, Cluster A symptomatology has been associated with increased neuroticism. Neuroticism is a personality trait characterized by increased stress vulnerability and propensity to experience negative affect, and has been considered a potential trait marker and risk factor for depression (Kendler et al., 2004; Roberts and Kendler, 1999). Consistent with this assumption, recent findings indicate that individuals with high levels of neuroticism are more sensitive to the adverse effects of stress (Kendler et al., 2004). Of primary importance for the present findings, Daley et al. (1998) found in a prospective study that Cluster A and B (but not Cluster C) symptoms were associated with increased episodic stress and interpersonal chronic stress, which in turn were linked to subsequent depression. Thus, in the Daley et al. (1998)'s study, the effect of Cluster A pathology on subsequent depression was mediated by stress. Our findings indicate that enduring Cluster A comorbidity predicts elevated perceived stress following antidepressant treatment and is in line with this prior study, raising the possibility that among subjects with depressive symptomatology, comorbid Cluster A pathology may result in poorer outcome through stress exacerbation. Future studies should directly test whether elevated neuroticism in MDD subjects with Cluster A comorbidity might predispose them to experience more life stressors and/or react more poorly to them.

A second, not mutually exclusive, factor explaining a specific link between Cluster A comorbidity and increased stress appraisal might be related to the pervasive interpersonal impairments characteristic of subjects with Cluster A pathology. According to the DSM-IV-TR (American Psychiatric Association, 2000), individuals with schizoid PD are characterized by a persistent pattern of detachment from social relationships

resulting in emotional coldness, detachment, or flattened affectivity in interpersonal situation, a tendency to prefer solitary activities, and a lack of close friends or confidants. In a similar vein, individuals with schizotypal PD prototypically feature a pervasive pattern of social and interpersonal deficits characterized by discomfort with close relationships, and also often lack close friends or confidants. Finally, the enduring distrust and suspiciousness of others, and the reluctance to confide in others characteristic of Paranoid PD also point to considerable impairments in interpersonal situations. Interestingly, in the present study, MDD subjects with enduring Cluster A comorbidity, but not those with Cluster B or C comorbidity, had a significantly lower percentage of married individuals, a pattern that might reflect interpersonal impairments in Cluster A.

When considered in a larger context, these interpersonal impairments may lead to diminished (or absent) social support in periods of distress, which in turn might have deleterious consequences. In fact, social support has been associated with decreased stress responsiveness, including reduced cortisol levels after a psychosocial stressor (Heinrichs et al., 2003) and lower psychological distress after negative life events (Ystgaard et al., 1999). Likewise, in MDD subjects, low levels of social support have been associated with the onset of depressive symptoms (Wade et al., 2000), greater depressive symptoms (Romanov et al., 2003), delayed recovery after a MDE (Zuroff and Blatt, 2002), and depression chronicity (Lynch et al., 1999). Clearly, future studies will be required to test the hypothesis that increased levels of perceived stress in MDD subjects with Cluster A comorbidity may be partially mediated by the lack of social support. Moreover, in light of the observation that most PD are characterized by elevated neuroticism (e.g., Morey et al., 2002; Trull and Durrett, 2005), it is possible that the

interaction of high neuroticism and low social support characterizing Cluster A PD may provide a diathesis for higher stress levels, and, perhaps, poor outcome and future relapse.

Several limitations of the present study should be acknowledged. First, stress appraisal was assessed using a single measure, the Perceived Stress Scale (Cohen et al., 1983). Although this scale has been found to reliably predict stress-related psychological symptoms, physical symptoms, and health service utilization (Cohen et al., 1983), we did not assess independently the types and severity of potential stressors. Second, MDD subjects with a history of current or recent substance abuse, psychosis, or severe antisocial PD were excluded from the present study; whether the present findings will extend to more severely MDD samples awaits empirical test. Third, a categorical approach based on the DSM was used to diagnose PD, and recent evidence suggests that a dimensional approach that considers personality as varying along a continuum might be more appropriate (Skodol et al., 2005; for reviews, see Trull and Durrett, 2005). Finally, the treatment plan did not involve a placebo arm, preventing us to assess whether some of the present findings were in fact due to non-specific, placebo effects. Although the specificity of the main findings linking Cluster A and elevated post-treatment PSS scores speaks against the possibility of a large role of placebo effects, future studies should incorporate a placebo arm.

These limitations notwithstanding, the present findings indicate that enduring Cluster A comorbidity in a well-characterized MDD outpatient sample predicted elevated perceived stress following an 8-week open-label treatment with fluoxetine. MDD patients with Cluster A comorbidity might therefore benefit from treatment approaches involving

a stress management program (e.g., Fava et al., 1991). The putative mediating role of elevated neuroticism and reduced social support on elevated stress appraisal in Cluster A comorbidity also warrants future scrutiny.

Tables

Table 1. *Pre-treatment ("pre") and post-treatment ("post) HAMD-17 and perceived stress scale (PSS) scores as a function of presence vs. absence of DSM-III-R PD clusters*

		Cluster A			Cluster B			Cluster C		
		Mean (SD)	t-value	P	Mean (SD)	t-value	P	Mean (SD)	t-value	P
HAMD-17: Pre	Yes:	19.98 (3.56) (n = 42)	2.44	0.016	20.80 (3.86) (n = 40)	3.72	0.0003†	20.24 (3.43) (n = 120)	3.76	0.0002†
	No:	18.60 (2.75) (n = 93)			18.60 (2.75) (n = 93)			18.60 (2.75) (n = 93)		
HAMD-17: Post	Yes:	10.31 (5.83) (n = 42)	2.22	0.028	10.85 (7.22) (n = 40)	2.48	0.014	10.22 (6.74) (n = 120)	2.60	0.01
	No:	7.96 (5.65) (n = 93)			7.96 (5.65) (n = 93)			7.96 (5.65) (n = 93)		
PSS score: Pre	Yes:	36.28 (6.72) (n = 36)	0.82	0.413	40.56 (5.92) (n = 34)	4.35	0.0005†	38.01 (6.86) (n = 101)	2.81	0.006
	No:	35.25 (5.91) (n = 76)			35.25 (5.91) (n = 76)			35.25 (5.91) (n = 76)		
PSS score: Post	Yes:	28.50 (7.70) (n = 34)	3.01	0.003†	29.06 (9.37) (n = 31)	3.03	0.003†	27.31 (9.38) (n = 98)	2.86	0.005†
	No:	23.09 (8.83) (n = 64)			23.09 (8.83) (n = 64)			23.09 (8.83) (n = 64)		

† $p<0.05$ after Bonferroni correction

Perceived Stress and Cognitive Vulnerability Mediate the Effects of Personality Disorder Comorbidity on Treatment Outcome in Major Depressive Disorder: A Path Analysis Study

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Abstract

Background. Although personality disorder (PD) comorbidity has been associated with poor treatment outcome in major depressive disorder (MDD), little is known about mechanisms mediating this link. Converging evidence suggests that maladaptive cognitive patterns, particularly in interaction with stressors, might lead to poor treatment outcome in MDD subjects with PD pathology. The goal of this study was to test the role of PD comorbidity, cognitive vulnerability, and perceived stress in treatment outcome in MDD.

Methods. Three hundred eighty-four MDD outpatients were enrolled in an 8-week open-label treatment of fluoxetine.

Results. Structural equation modeling and path analyses revealed that the effect of PD vulnerability on treatment outcome was fully mediated by increased pre-treatment cognitive vulnerability and depression severity, which led to increased stress perception after treatment and poorer antidepressant response.

Conclusions. Depressogenic cognitions might be continuously activated by chronic distress in MDD subjects reporting Axis II pathology, leading to stress exacerbation and eventually poorer treatment outcome.

Introduction

Studies indicate that 20-50% of inpatients and 50-85% of outpatients with a current major depressive disorder (MDD) meet criteria for one or more personality disorders (PDs) (Yen et al., 2006). These high rates of PD comorbidity underscore the need to better understand the link between these disorders and evaluate the potential implications of PD comorbidity on MDD.

Although inconsistencies among studies abound, the presence of PD comorbidity is generally hypothesized to have adverse effects on the course and treatment of MDD. In line with this hypothesis, comorbid PD in MDD has been associated with: longer time to achieve treatment response (Pilkonis and Frank, 1988); higher rates of relapse (Hart et al., 2001; Ilardi et al., 1997); shorter time to recurrence (Cyranowski et al., 2004); chronicity (Riso et al., 1996); and poorer response to antidepressant treatment (e.g., Peselow et al., 1992; Sato et al., 1993).

Several studies, however, did not find a link between comorbid PD and poor treatment response (Fava et al., 1994, 1997, 2002; Mulder et al., 2003), and recent reviews have challenged the view that comorbid PD negatively impact treatment outcome in depression (e.g., Kool et al., 2005). A recent meta-analysis involving the highest numbers of studies (n = 34) and patients (1663 MDD subjects with comorbid PD and 1860 MDD subjects without comorbid PD) found, however, that comorbid PD was associated with a double risk of poor outcome, irrespective of treatment modality (drugs, psychotherapy, or combined treatment) (Newton-Howes et al., 2006).

Although many, albeit not all, studies have shown a link between PD comorbidity and poor treatment outcome in MDD, it is important to stress that the *causal mechanisms*

or *mediating variables* underlying this association remain largely unknown. A greater understanding of mechanisms underlying the relationship between personality pathology and the course of MDD might not only help in reconciling inconsistent findings in the literature but could also inform the development of more efficacious treatment approaches.

Diathesis-stress theories of depression might provide a powerful framework for identifying mediating variables underlying links between comorbid PD and poor treatment outcome in depression. In general, diathesis-stress theories postulate that specific factors predispose individuals to develop depression when confronted with negative life stress (Gotlib and Hammen, 2002). Among various diatheses, the role of cognitive vulnerabilities in the etiology and course of depression has received substantial empirical scrutiny. According to cognitive theories of depression, an individual's interpretation of negative events increases his/her vulnerability to developing and maintaining depression after these events occur (Abramson et al., 1989; Beck, 1967). Beck's cognitive theory of depression, in particular, proposes that dysfunctional attitudes - rigid and extreme beliefs about the self, the future, and the world that often entail themes of deriving one's worth from being perfect or needing approval from others - are activated in response to specific stressors, leading to an increased likelihood to develop depression (Beck et al., 1979).

A convergence of several lines of evidence raises the possibility that maladaptive cognitive patterns, in particular *in interaction with stressors*, might lead to poor treatment outcome in MDD subjects with PD comorbidity. First, irrespective of depressive status, PDs have been associated with elevated dysfunctional attitudes (e.g. Ilardi and Craighead,

1999; O'Leary et al., 1991), which in turn have been shown to negatively impact the course and treatment of depression (e.g. Alloy et al., 2006; Dunkley et al., 2006; Riso et al., 2003; Thase et al., 1992). Of primary relevance to the present study, elevated dysfunctional attitudes *at baseline* predicted poor response to both psychological (e.g. Scott and Harrington, 1996) and pharmacological (e.g. Fava et al., 1994; Zuroff et al., 1999) treatments. Among clinically depressed subjects, those with PD comorbidity have been found to report significantly higher dysfunctional attitude scores than depressed subjects without PD comorbidity (Marton et al., 1989). Thus, dysfunctional attitudes and depressogenic cognitive patterns might be important mediating variables influencing treatment outcome in MDD subjects with PD comorbidity.

Second, PDs predispose individuals to the experience of negative life events (American Psychiatric Association, 1994), and are characterized by increased stress reactivity. In a community sample, for example, Daley et al. (1998) found that PD symptoms predicted interpersonal chronic stress and self-generated episodic stress over 2 years, which in turn increased the risk for depression. These findings are important, particularly since environmental factors, including life stressors, have been found to potentiate the effects of cognitive dysfunctions. Accordingly, in both clinical (e.g. Lewimsohn et al., 2001) and non-clinical (e.g., Flett et al., 1995) samples, dysfunctional attitudes have been found to interact with stressful life events to prospectively predict depressive symptoms or onset of depression. Of interest, recent studies suggest that dysfunctional attitudes (1) fully mediated the relation between depressive symptoms and stressors (Church et al., 2005); and (2) influenced both *actual* and *perceived* daily stress, which in turn predicted depressive symptoms (Dunkley et al., 2003). Overall, these

findings suggest that individuals endorsing depressogenic cognitive styles are more likely to make negative inferences in response to negative life events, in turn increasing their vulnerability to depression (Abramson et al., 1989; Beck, 1967). Moreover, stress perception appears to be an important mediator explaining the relationship between dysfunctional attitudes and depressive symptoms (Dunkley et al., 2003).

The present study

Based on the literature reviewed above, we hypothesized that three factors - PD vulnerability, cognitive vulnerability, and stress exacerbation - would influence treatment outcome in MDD. Specifically, we expected that (1) certain personality traits would be linked to increased cognitive vulnerability; (2) cognitive vulnerability would lead to increased stress appraisal after the treatment; and (3) increased stress appraisal (as well as increased depression severity) would lead to poor treatment outcome. These hypotheses were incorporated within a model postulating that maladaptive cognitive patterns leading to increased stress exacerbation mediated the effects of PD comorbidity on treatment outcome (Fig. 1). Structural equation modeling and path analyses were used to test these hypotheses and the possible causal relations among PD vulnerability, cognitive vulnerability, perceived stress and treatment outcome.

Methods

Participants

The current study presents new findings from a larger study that evaluated the efficacy of an 8-week open-label treatment of fluoxetine 20 mg/day for MDD. The parent study was conducted at the Depression Clinical and Research Program (DCRP) at Massachusetts General Hospital (MGH) (Fava et al., 2002; Farabaugh et al., 2002, 2006), and included 384 outpatients between the ages of 18 and 65. All enrolled subjects met criteria for MDD, as assessed with the Structured Clinical Interview for DSM-III-R, Patient Edition (SCID-P; Spitzer et al., 1989), and had a score of ≥ 16 on the 17-item Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960) at baseline. The following conditions led to exclusion from the study: pregnancy, breast-feeding, use of birth control, suicide risk, history of neurological illness, serious unstable medical illness, organic mental disorders, substance abuse during the last year, schizophrenia, delusional disorder, bipolar disorder, severe antisocial personality disorder, and mood-congruent or incongruent psychotic features. Subjects were also excluded if they reported: (1) a history of multiple adverse drug reactions; (2) non-response to or intolerance of fluoxetine (60-80 mg/day); (3) failure to respond to at least one adequate antidepressant treatment during their current major depressive episode; (4) current use of other psychotropic drugs; and (5) hypothyroidism. Throughout the acute treatment, subjects were seen biweekly for safety and efficacy assessments.

The study protocol and procedures were approved by the MGH Institutional Review Board; participants provided written informed consent before entering the study.

Clinical assessments and questionnaires

The main goal of the present study was to evaluate possible causal relations among PD vulnerability, cognitive vulnerability, perceived stress, and treatment outcome in MDD. To this end, both before and immediately after the 8-week treatment, subjects were administered the self-rated Perceived Stress Scale (PSS; Cohen et al., 1983), the Dysfunctional Attitude Scale (DAS; Weissman and Beck, 1978), and the Cognitions Questionnaire (CQ; Fennell and Campbell, 1984) to assess individual differences in stress appraisal, dysfunctional attitudes, and depressive cognitive style, respectively. To assess the presence of any PD, the SCID-II (including its screening questionnaire) (First et al., 1997) was administered at both time points. All clinical assessments (SCID-P, SCID-II, and HRSD) were carried out by clinicians fully trained in their administration.

The PSS has been widely used in the literature to assess the degree to which participants appraise their daily life as unpredictable, uncontrollable, and overwhelming (e.g., "*In the last week, how often have you felt that you were unable to control the important things in your life?"*). Prior research has shown that this scale better predicts stress-related psychological symptoms, physical symptoms, and health service utilization than commonly used life event scales (e.g., Cohen et al., 1983). This self-rated scale includes 14 items scored on a 5-point scale, and possesses satisfactory internal and short-term reliability (coefficient alpha reliability: 0.84; two-day test-retest reliability: 0.85; Cohen et al., 1983).

The DAS was developed to assess dysfunctional and rigid cognitions, which have been linked to the onset and maintenance of depression in Beck's cognitive theory of

depression (Beck, 1967). Specifically, this 40-item self-rated questionnaire assesses maladaptive attitudes, including perfectionistic standards of performance (e.g., *"If I fail at my work, then I am a failure as a person"*), sensitivity to social criticism and need for approval (e.g., *"If others dislike you, you cannot be happy"*), expectations of control (e.g., *"I should always have complete control over my feelings"*), and rigid ideas about the world. Each item is rated on a 7-point Likert scale ranging from *totally agree* to *totally disagree*. A total score and two scale scores (Perfectionism and Need for Social Approval) can be computed; in the present study, the total score was used. Higher scores indicate greater endorsements of dysfunctional beliefs. DAS scores, either alone or in conjunction with stressors, have been found to predict depressive symptoms (Hankin et al., 2004; Ilardi and Craighead, 1999), highlighting the validity of this scale. Satisfactory internal consistency (Cronbach's alpha 0.89) and test-retest reliability over an 8-week period (r=0.84) have been reported (Weissman and Beck, 1978). In the present sample, the test-retest reliability over the 8-week treatment period was satisfactory ($r = 0.70$, $p < 0.0001$, $n = 142$).

The CQ was developed to provide an overall measure of depressive cognitive style. This self-report measure has been derived from the revised learned helplessness model (Abramson et al., 1978), which conceptualizes depression as a response to negative events perceived as uncontrollable and attributed to stable and internal causes. Specifically, the CQ assesses five dimensions of negative thinking in relation to different types of hypothetical events and their consequences. The five dimensions probed are: emotional impact (e.g., aversiveness), attribution of causality, generalization across time, generalization across situations, and perceived uncontrollability.A total score providing

an overall measure of depressive distortions was used. Prior studies have shown that the total CQ score possesses satisfactory internal reliability and validity (Fennell and Campbell, 1984; MacLeod and Williams, 1990; Mitchell and Campbell, 1988). In the present study, the CQ scale had satisfactory test-retest reliability ($r = 0.66$, $p < 0.0001$, $n = 115$).

Statistics

To avoid the possibility that PD diagnoses may be confounded by the patient's depressed state (Fava et al., 1994, 2002; Zimmerman, 1994), the statistical analyses considered only MDD subjects who either (1) met DSM-III-R criteria for Cluster A (n = 42), Cluster B (n = 40), or Cluster C (n = 120) at *both* the pre- and post-treatment assessments; or (2) did not meet *any* PD criteria at either assessment (n = 93).

For the statistical analyses, three data analytic strategies were used. First, zero-order correlations between measures of depression (HRSD), cognitive vulnerability (DAS, CQ) and perceived stress (PSS) were computed to evaluate relations among the variables under investigation. Second, structural equation modeling and path analysis were used to assess the fit between: (1) models hypothesizing specific causal relations between PD vulnerability, cognitive vulnerability, stress perception, and treatment outcome, and (2) the observed set of correlations between the variables in the models. Note that the goal of the path analyses was not to test all possible models, but instead to test models derived from prior theories and empirical findings. Third, to test the specificity of findings emerging from the second step, path analyses were separately performed for Cluster A, Cluster B, and Cluster C PDs. For path analyses, PD vulnerability was entered as a

dichotomous variable (see Keith, 2006, for detail concerning the use of dichotomous variables in path analyses).

Fig. 1 shows an initial model postulating a specific causal flow from a latent exogenous variable (PD vulnerability) through two sets of intervening variables (first set: pre-treatment HRSD and cognitive vulnerability; second set: post-treatment PSS) to an outcome variable (post-treatment HRSD). Thus, this model postulates indirect effects of PD vulnerability on treatment outcome in MDD. The effects are mediated by cognitive vulnerability and depression severity before treatment leading to increased stress perception after the treatment, in turn modulating treatment outcome. Both PD vulnerability and cognitive vulnerability were defined as latent variables.

For path analyses, we utilized AMOS (Arbukle, 2003; version 5.0), which uses maximum-likelihood estimation to test the fit of a hypothesized model to the observed variance-covariance matrix. In line with the recommendation of Hoyle and Panter (1995), various measures of fit were utilized to evaluate various models. First, Chi-square (χ^2) was used to assess the statistical fit of the model; non-significant χ^2 means that the model and the actual data are consistent with one another. Next, we considered the ratio of the χ^2 value to the *df* in the model (absolute fit); ratios between 1 and 2 reflect better fitting models (Carmines and McIver, 1981). To assess incremental fit, the Comparative Fit Index (CFI) was used as a goodness of fit index (GFI). GFI provides an estimates of the total covariance accounted for by the model, and CFI values over 0.95 represent a good fit of the model to the data (Bentler, 1990). Finally, to assess parsimony-adjusted fit, we used the Root Mean Square Error of Approximation (RMSEA); values lower than 0.05 are interpreted as suggesting a close fit of the model (Browne and Cudeck, 1993).

Whereas the initial model postulated a full mediation of PD on treatment outcome, an alternate model was evaluated by adding direct paths from the exogenous latent variable (*PD vulnerability*) and the mediating variable (*Cognitive vulnerability*) to the outcome variables (*post-treatment HRSD*). Note that the initial model was nested in the alternate model (i.e., it can be derived from the other by deleting paths). Accordingly, the difference between the respective χ^2 values was computed to assess whether the initial and revised models fit the data differently. The Akaike Information Criterion (AIC) was utilized to evaluate competing models. Following prior recommendations (Keith, 2006), the model with the lower AIC value was favored.

Results

Zero-order correlations

Before conducting a path analysis, zero-order correlations were computed to determine whether the variables under investigation were related to each other. As shown in Table 1, most of the correlations were significant, justifying the use of path analysis.

Initial, fully mediated model

Fig. 1 illustrates the initial model postulating indirect effects of PD and cognitive vulnerability on treatment outcome in MDD and the resulting path coefficients. As shown in the figure, all standardized coefficients were significant and large (i.e., above 0.25; Keith, 2006). The path between pre-treatment HRSD and post-treatment PSS score was

also significant but in the moderate range. All fit indices indicated a good fit of the model to the data, χ^2= 11.06, p=0.85 (df =17; n=231), χ^2/df=0.65. The RMSEA was smaller than 0.001, with a 90% confidence interval of 0.000 to 0.034, and the CFI was 1.0. As shown in Fig. 1, PD vulnerability was significantly and positively correlated with pre-treatment cognitive dysfunctions and pre-treatment HRSD scores, which in turn were both significantly and positively correlated with increased stress perception after treatment. Elevated stress perception was positively correlated with depression severity after the 8-week treatment. Sobel's tests (Sobel, 1982) confirmed that the indirect path between PD vulnerability and post-treatment stress perception (Z = 4.43, p < 0.00001; mediating variable: cognitive vulnerability), and the indirect path between cognitive vulnerability and treatment outcome (Z = 2.75, p < 0.007; mediating variable: post-treatment stress perception) were both significant. Thus, the effect of PD vulnerability on treatment outcome was fully mediated by increased cognitive vulnerability and depression severity, leading to increased stress exacerbation after treatment. Table 2 summarizes the effect coefficients for the initial model.

Revised model

The initial model does not include direct paths between (1) *PD vulnerability* and *post-treatment PSS*; (2) *PD vulnerability* and *post-treatment HRSD*; and (3) *Cognitive vulnerability* and *post-treatment HRSD*. The initial, fully mediated, and over-identified model was compared to a revised, just-identified model including these three additional paths. The revised model fit the data equally well (χ^2=9.30, p=0.81, df=14, n=231, χ^2/df=0.66; RMSEA<0.001, 90% confidence interval: 0.000-0.041; CFI = 1.00). A test of

the difference between the two competing models indicated that the initial model did not fit the data significantly less well than the just-identified revised model ($\Delta\chi^2$=1.76, df=3, p=0.62). Following established procedures (Keith, 2006), the initial model was favored because (1) was more parsimonious (df=17) than the revised model (df=14), and (2) had an equivalent fit. Evaluation of the critical ratio (t=coefficient/$SE_{coefficient}$) for the additional direct paths leads to a similar conclusion in favor of the initial model. In fact, the critical ratio for the path between *PD vulnerability* and post-treatment *PSS*, (t =1.94, p=0.23); *PD vulnerability* and post-treatment *HRSD* (t=-0.36, p=0.72); and *Cognitive vulnerability* and post-treatment *HRSD* (t=0.02, p=0.98) indicated that these paths were not significant. Finally, the Akaike Information Criterion (AIC) was lower for the initial model, again consistent with the notion that the model without direct path should be favored.

Cluster-specific model

To assess whether the initial model was specific to a given DSM-based PD cluster, a path analysis of the initial model was performed for Cluster A, Cluster B, and Cluster C separately. For each cluster, the model provided a good fit of the data (Cluster A: χ^2=2.18, p=0.90, df=6, χ^2/df=0.36; RMSEA<0.001; CFI=1.0; Cluster B: χ^2=7.46, p=0.28, df=6, χ^2/df=1.24; RMSEA=0.043; CFI=0.99; Cluster C: χ^2=6.91, p=0.33, df=6, χ^2/df=1.15; RMSEA=0.027; CFI=0.996). For each cluster, the direct path between PD and post-treatment PSS was not significant (Table 3). Interestingly, only for Cluster A, a fully mediated model was observed (Fig. 2). For both Cluster B and C, the path

coefficient between cognitive vulnerability and post-treatment PSS was not significant (Table 3).

Discussion

In recent years, inconsistent findings have emerged around the question of whether PD comorbidity might have adverse effects on the course and treatment of MDD (Mulder, 2006; Kool et al., 2005; Newton-Howes et al., 2006). Although several studies have shown a link between PD comorbidity and poor treatment outcome in MDD (Newton-Howes et al., 2006), little is known about causal mechanisms or mediating variables underlying this link. The main goal of the present study was to evaluate the effects of potential mediating variables on treatment outcome after an 8-week open-label treatment with fluoxetine in a clinical sample characterized by substantial PD comorbidity. Based on prior findings, we hypothesized that maladaptive cognitive patterns and increased stress appraisal might mediate the effects of PD on treatment outcome. These hypotheses were confirmed. Specifically, path analyses revealed that PD comorbidity significantly and positively correlated with cognitive vulnerability (dysfunctional attitudes and depressogenic cognitive patterns), which in turn was positively correlated with stress appraisal after the treatment; increased stress perception was in turn significantly and positively correlated with depression severity after treatment. Notably, a fully mediated model was compared with a partially mediated model that included direct paths between: (1) PD and treatment outcome; (2) PD and stress perception; and (3) cognitive vulnerability and treatment outcome. The partially

mediated model was not a significantly better fit to the data than the fully mediated model, and the additional three paths, including the one between PD and treatment outcome, were not significant. Moreover, Sobel's tests confirmed that the indirect path between PD vulnerability and post-treatment stress perception and the one between cognitive vulnerability and treatment outcome, were significant. Together with the presence of non-significant direct paths, findings from the Sobel's tests indicate that the relation between PD and treatment outcome can be considered fully mediated (Dunkley et al., 2006). Interestingly, although each DSM-based PD cluster was associated with elevated cognitive vulnerability, the path coefficient between pre-treatment cognitive vulnerability and post-treatment perceived stress was significant only for Cluster A, indicating that the fully mediated model provided an excellent statistical fit for MDD subjects reporting enduring Cluster A pathology (paranoid, schizoid, and schizotypal PD).

The present findings implicate cognitive vulnerability and perceived stress in the mediation of treatment outcome for MDD subjects presenting with enduring personality pathology. These results are consistent with and extend a large body of prior work. First, PDs are characterized by deeply ingrained and inflexible patterns of relating, perceiving, and thinking (DSM-IV, APA, 1994), and prior studies have documented elevated dysfunctional attitudes in subjects with Axis II pathology (e.g. Ilardi and Craighead, 1999; O'Leary et al., 1991). According to cognitive theories of depression, and in particular Beck's cognitive theory, maladaptive, negatively focused cognitive schemata involving themes of failure, personal inadequacy, and hopelessness about the self, the world, and the future are activated in response to specific stressors, leading to an

increased likelihood to develop depression (Abramson et al., 1989; Beck, 1967, Beck et al., 1979). Consistent with this hypothesis, a multitude of studies have found that dysfunctional attitudes and depressogenic cognitive patterns influence the onset and course of depression. In prospective studies, for example, individuals endorsing dysfunctional attitudes and negative cognitive style experienced more episodes, more severe episodes, and more chronic courses of depression during a 2.5-year follow-up period compared to control subjects (e.g. Alloy et al., 2006). Similarly, in a clinical sample characterized by substantial PD comorbidity, DAS (perfectionism) scores predicted depressive symptoms 3 years later (Dunkley et al., 2006). Of primary relevance to the present study, elevated dysfunctional attitudes *at baseline* predicted poor response to both psychological (Jarret, et al., 1991; Scott and Harrington, 1996) and pharmacological (Fava et al., 1994; Zuroff et al., 1999) treatments. Finally, elevated dysfunctional attitudes have been related with early onset and longer duration of depression (Luty et al., 1999), increased risk for relapse (e.g. Thase et al., 1992), and chronic course (Riso et al., 2003). Findings emerging from the present study are consistent with these prior reports and indicate that the presence of elevated dysfunctional attitudes and depressogenic cognitions before treatment predict higher depressive symptoms after an 8-week fluoxetine treatment in MDD subjects reporting PD comorbidity.

Interestingly, in the present study, the effect of cognitive vulnerability on treatment outcome was mediated by increased stress perception after the treatment. Accordingly, MDD subjects with Axis II pathology reporting rigid and extreme beliefs about the self and the world before the treatment reported higher level of stress, which in turn was

associated with higher depressive symptoms after the treatment. These findings are intriguing, particularly since cognitive vulnerability models have suggested that maladaptive cognitive schemata may remain latent until primed by a distress or negative life event (e.g., Ingram et al., 1998; Miranda and Persons, 1988), and activation of cognitive vulnerability during follow-up periods has been hypothesized to contribute to relapse and recurrence of depression (Segal et al., 1992). Because PD is characterized by chronic, clinically significant distress (American Psychiatric Association, 1994, p. 633), it is possible that depressogenic cognitions are continuously primed and activated in MDD subjects reporting enduring Axis II pathology, leading to poor treatment outcome.

In the current study, presence of any DSM-based PD cluster was associated with increased cognitive vulnerability. Only for MDD subjects with Cluster A comorbidity, however, elevated dysfunctional attitudes and depressogenic cognition at baseline predicted increased stress perception after the treatment, indicating that the fully mediated model provided an excellent fit only for Cluster A. These findings are intriguing, particularly in light of prior evidence that symptoms of Cluster A (as well as Cluster B, but not Cluster C) pathology predicted interpersonal chronic stress and self-generated episodic stress over 2 years, which in turn increased the risk for depressive symptoms (Daley et al., 1998). Although stress mediated the relationship between Cluster A pathology and later symptoms of depression in both the present and Daley et al.'s (1998) study, it is important to emphasize that the reasons for this specificity are not entirely clear and that prior studies investigating the effects of DSM-based PD pathology on treatment outcome in depression have yielded somewhat inconsistent findings (e.g., Daley et al., 1999; Hart et al., 2001; Ilardi et al., 1997; Peselow et al., 1992). One

possibility is that the emotional withdrawal, lack of warmth, and odd/eccentric behavior characteristic of Cluster A pathology may lead to restricted social support, which is an important buffer against the physiological (Heinrichs et al., 2003) and psychological (Ystgaard et al., 1999) effects of stress. Although the present findings await replication from future studies, they suggest that the link between cognitive vulnerability and stress exacerbation might be particularly important for MDD subjects reporting Cluster A comorbidity.

The limitations of the present study deserve mention. First, a key mediating variable (post-treatment stress appraisal) and the outcome variable (post-treatment HRSD) were measured concurrently. Accordingly, the present findings cannot demonstrate any causal relation between increased stress perception and depressive symptoms after the treatment. It is possible that depressive symptoms influenced stress perception, or that bidirectional relations exist between these variables. To assess causality, prospective designs assessing mediating variables and outcome variables at different time points will be required. Second, we did not investigate single PD diagnoses or subgroups of patients differing in clinical and sociodemographic variables that have been associated with differential treatment response (e.g., Fava et al., 1997). Although conceptually of great interest, subgrouping would have produced sample sizes too small for the SEM analyses. Moreover, the use of DSM-based clusters has received support in several factor and cluster-analytic studies (e.g., Bagby et al., 1993). Third, although the present SEM provided an excellent fit to the data, it is important to keep in mind that it is always possible that other models not tested in the present study might fit the data equally well or even better. The present model was, however, developed based on prior empirical

findings and current etiological theories of depression, and the findings confirmed the *a priori* hypotheses. Fourth, analyses were primarily based on self-report assessments. Although the questionnaires utilized in the present study have been widely used in the literature and possess satisfactory reliability and validity, reporting biases cannot be excluded. Finally, in light of the rather extensive exclusion criteria used in the current study, future work should evaluate the generalizability of the present findings to community samples, which will likely be more heterogeneous.

In spite of these limitations, the present findings indicate that the relation between PD and treatment outcome was fully mediated by intervening variables. Specifically, the SEM analyses revealed that the presence of PD comorbidity was associated with increased maladaptive cognitive patterns (dysfunctional attitudes and depressogenic cognitions) leading to elevated stress appraisal after the treatment, which in turn was associated with higher depression severity after an 8-week fluoxetine treatment. More generally, the present findings underscore the need to address underlying cognitive and personality vulnerability, in addition to symptoms of depression, in treatments for depression (Hayes et al., 1996; Zuroff et al., 1999).

Figures

Fig. 1: Initial, fully mediated model postulating indirect effects of personality vulnerability and cognitive vulnerability on treatment outcome in MDD. Ovals depict latent (unmeasured) variables (personality vulnerability and cognitive vulnerability), whereas rectangles symbolize measured variables. Straight arrows depict paths (presumed influences). The letters "d" denote "disturbances" (i.e., residual errors). For disturbances, a coefficient equal to 1 was selected so that the residual errors had the same scale of measurement as the respective measured variables (Keith, 2006). HRSD: Hamilton Rating Scale for Depression (Hamilton, 1960); DAS: Dysfunctional Attitude Scale (Weissman and Beck, 1978); CQ: Cognitions Questionnaire (Fennell and Campbell, 1984); PSS: Perceived Stress Scale (Cohen et al., 1983). The subscript "pre" and "post" denote pre-treatment and post-treatment scores, respectively.

Fig. 2: Fully mediated model investigating the effects of Cluster A PD comorbidity, cognitive vulnerability, baseline depression severity, and perceived stress on treatment outcome. See Figure 1 for more details.

Figure 1

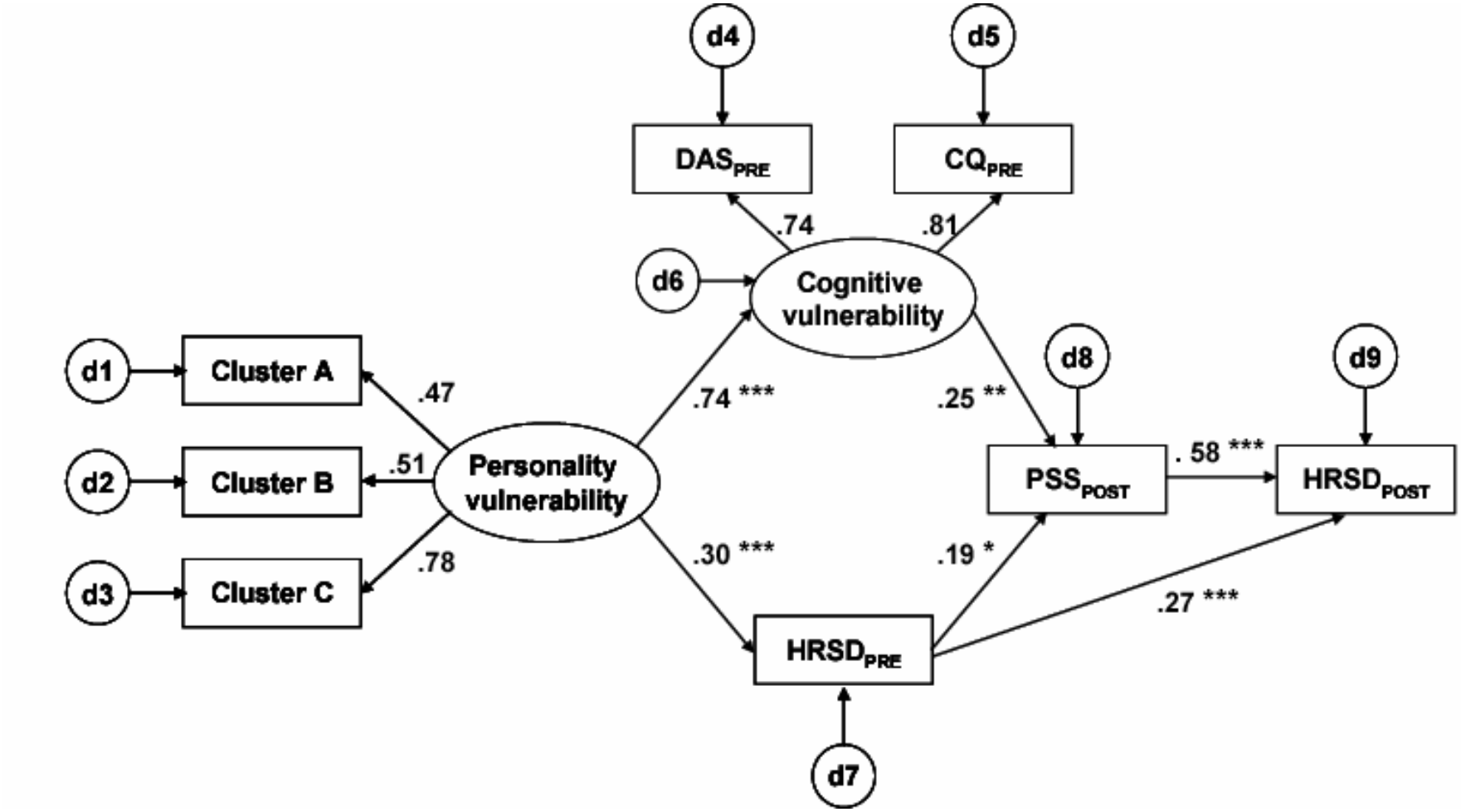
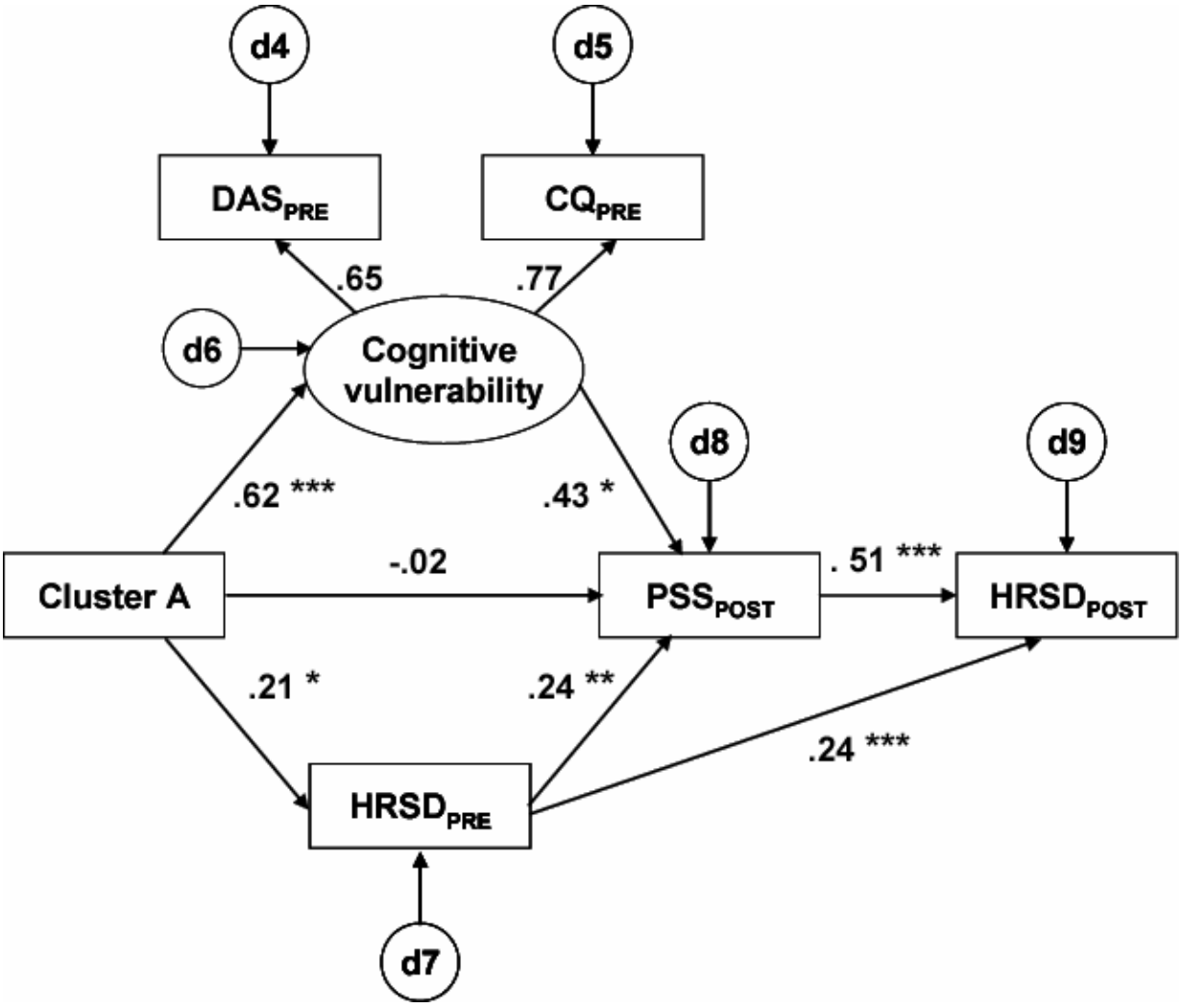

d4
d5
DAS PRE
CQ PRE
.74
.81
d6
Cognitive vulnerability
d1
Cluster A
.47
.74 ***
.25 **
d8
d9
d2
Cluster B
.51
Personality vulnerability
PSS POST
. 58 ***
HRSD POST
d3
Cluster C
.78
.30 ***
.19 *
.27 ***
HRSD PRE
d7

Figure 2


d4
d5
DAS PRE
CQ PRE
.65
.77
d6
Cognitive vulnerability
d8
d9
.62 ***
.43 *
Cluster A
-.02
PSS POST
. 51 ***
HRSD POST
.21 *
.24 **
.24 ***
HRSD PRE
d7

Tables

Table 1: Zero-order correlations among the variables under investigation.

	Pre-treatment HRSD	Pre-treatment DAS	Pre-treatment CQ	Post-treatment PSS	Post-treatment HRSD
Pre-treatment HRSD	1.000	0.214**	0.180*	0.260***	0.407***
		(n = 160)	(n = 139)	(n = 172)	(n = 231)
Pre-treatment DAS		1.000	0.589***	0.135	0.154
			(n = 132)	(n = 138)	(n = 160)
Pre-treatment CQ			1.000	0.258**	0.161
				(n = 118)	(n = 139)
Post-treatment PSS				1.000	0.655***
					(n = 172)
Post-treatment HRSD					1.000
Mean	19.52	147.86	28.19	25.87	9.41
S.D.	3.32	35.71	11.10	9.37	6.40
N	231	160	139	172	231

Note: HRSD: Hamilton Rating Scale for Depression (Hamilton, 1960); DAS: Dysfunctional Attitude Scale (Weissman and Beck, 1978); CQ: Cognitions Questionnaire (Fennell and Campbell, 1984); PSS: Perceived Stress Scale (Cohen et al., 1983)

***p<0.001, **p<0.01, *p<0.05

Table 2: Effect coefficients for the initial model postulating indirect effects of personality and cognitive vulnerability on treatment outcome (post-treatment HRSD).

Variable	Direct	Indirect	Total
Personality vulnerability	--	0.219	0.219
Cognitive vulnerability	--	0.146	0.146
Pre-treatment HRSD	0.267	0.107	0.374
Post-treatment PSS	0.576	0.000	0.576

Note: Direct, indirect, and total effects were calculated after standardizing all variables. Personality vulnerability and cognitive vulnerability were entered as latent variables. HRSD: Hamilton Rating Scale for Depression (Hamilton, 1960); PSS: Perceived Stress Scale (Cohen et al., 1983). For personality vulnerability and cognitive vulnerability, no direct effects on treatment outcome were postulated.

Table 3: Standardized regression weights emerging from the cluster-specific path analyses.

			Cluster A	Cluster B	Cluster C
Personality vulnerability	→	Cognitive vulnerability	0.622***	0.703***	0.566***
Personality vulnerability	→	Pre-treatment HRSD	0.207*	0.309***	0.251***
Pre-treatment HRSD	→	Post-treatment PSS	0.236**	0.211*	0.191**
Cognitive vulnerability	→	Post-treatment PSS	0.429*	0.307	0.189
Personality vulnerability	→	Post-treatment PSS	-0.016	-0.018	0.076
Pre-treatment HRSD	→	Post-treatment HRSD	0.244***	0.276***	0.257***
Post-treatment PSS	→	Post-treatment HRSD	0.510***	0.545***	0.580***

Note: HRSD: Hamilton Rating Scale for Depression (Hamilton, 1960); DAS: Dysfunctional Attitude Scale (Weissman and Beck, 1978); CQ: Cognitions Questionnaire (Fennell and Campbell, 1984); PSS: Perceived Stress Scale (Cohen et al., 1983)

***p<0.001, **p<0.01, *p<0.05

GENERAL CONCLUSION

The overarching goal of the current work was to investigate the potential role of PD comorbidity on treatment outcome in major depression. Specifically, the aim of **Study 1** was to evaluate whether the presence of stable PDs – conditions characterized by enduring and pervasive dysfunctional patterns of cognition, affect, and interpersonal relations – predicted stress appraisal following an 8-week open-label treatment with fluoxetine in an MDD outpatient sample. The aim of **Study 2** was to test precise mechanisms (specifically, cognitive vulnerability and stress appraisal) that might mediate links between PD comorbidity and treatment outcome in major depressive disorder.

These studies were inspired by a large body of work indicating that:

1) Stressors and elevated stress appraisal play an important role in the etiology and persistence of depression (**Section I**);
2) Cognitive vulnerabilities involving rigid and dysfunctional attitudes and maladaptive attributional styles increase risk for depression, particularly in interaction with stressors (**Sections I**);
3) PDs are characterized by deeply ingrained and inflexible patterns of relating, perceiving, and thinking (DSM-IV, APA, 1994), and have been associated with (a) elevated dysfunctional attitudes; and (b) increased stress generation and reactivity (**Section II**).

A convergence of these independent lines of evidence led to the core hypothesis of the present work: PD vulnerability, cognitive vulnerability, and stress exacerbation negatively influence treatment outcome in MDD. Specifically, we postulated that (1) PD

would be associated with increased cognitive vulnerability; (2) cognitive vulnerability would lead to exaggerated stress perception following treatment; and (3) exaggerated stress perception would eventually lead to worse treatment outcome. Using a combination of statistical approaches, we largely confirmed these hypotheses.

In **Study 1**, multiple regression analyses revealed that the presence of stable Cluster A, but not Cluster B or C, pathology was associated with higher levels of perceived stress after pharmacological treatment. These findings emerged even after adjustments for baseline depression severity and perceived stress as well as various sociodemographic variables, suggesting that stress exacerbation might be a critical factor associated with poor treatment outcome in MDD subjects with Cluster A pathology.

In **Study 2**, structural equation modeling and path analyses indicated that PD comorbidity was positively correlated with cognitive vulnerability, which in turn was associated with elevated stress appraisal after the pharmacological intervention. Elevated stress perception, in turn, was significantly linked to depression severity after the treatment. Two additional findings were of interest. First, the relation between PD and treatment outcome was fully mediated through cognitive vulnerability and stress appraisal. Second, the fully mediated model was found only for MDD subjects who exhibited enduring Cluster A pathology.

Collectively, findings of the present studies highlight important mediating variables (cognitive vulnerability and stress appraisal) that might explain links between PD comorbidity and poor course and treatment of MDD and might help to resolve inconsistencies in the literature (Fava et al., 1994, 1997, 2002; Mulder, 2006; Kool et al., 2005; Newton-Howes et al., 2006).

In both studies, presence of Cluster A pathology (paranoid, schizoid, and schizotypal PD) was uniquely associated with stress exacerbation and the mediating effect of cognitive vulnerability on treatment outcome. These findings are intriguing, particularly in relation to prior studies. Compared with other DSM clusters, Cluster A pathology has been associated with the worst social functioning 12 years later, particularly in domains involving interpersonal relationships and perception of stress and strain (Seivewright et al., 2004). Compared with Cluster C, Cluster A (and B) has also been associated with significantly lower quality of life ratings and significantly higher rates of attempted suicide (Brieger et al., 2002). Along similar lines, Daley et al. (1998) found that Cluster A (as well as B) symptoms were linked to increased episodic stress and interpersonal chronic stress, which in turn predicted subsequent depression.

As discussed in more detail in **Section III**, several factors might explain the specific link among Cluster A comorbity, stress exacerbation, and the mediating effect of cognitive vulnerability on treatment outcome. First, multiple studies have shown that Cluster A is characterized by elevated levels of neuroticism (Blais, 1997; Camisa et al., 2005; Costa and McCrae, 1990; Gurrera et al., 2005), a personality trait associated with increased (a) stress generation and reactivity and (b) vulnerability to depression (Fava and Kendler, 2000; Kendler et al., 2004). Second, Cluster A pathology is characterized by considerable interpersonal impairments. Schizoid, schizotypal, and paranoid PD are characterized by pervasive social detachment and emotional coldness; strong discomfort with close relationships; and enduring distrust and suspiciousness, respectively. As we have argued in **Section III**, such interpersonal impairments may lead to a lack of social support during stressful periods. This in turn may increase the risk for future depressive

episodes, since several studies have shown that individuals embedded in socially supportive networks are less likely to exhibit mental health difficulties, including depression (Uchino et al., 2006). Moreover, individuals perceiving social support from others might be less negatively affected by stressors that lead to depression (Paykel, 1994). Consistent with the hypothesis that a lack of social support in Cluster A pathology might mediate poorer outcome, studies have reported that social support can have protective effects on (1) both biological (Heinrichs et al., 2003) and psychological (Ystgaard et al., 1999) aspects of the stress response; and (2) the course and outcome of depression (Lynch et al., 1999; Romanov et al., 2003; Wade et al., 2000; Zuroff and Blatt, 2002).

Implication for Treatment Approaches

Findings from the present studies emphasize the role of cognitive vulnerability and stress appraisal on treatment outcome in MDD subjects with PD comorbidity treated with a standard antidepressant. These findings are consistent with theories that have recognized the critical role of dysfunctional attitudes and maladaptive cognitive patterns on treatment outcome and that have advocated the use of cognitive therapy for depressed patients with comorbid PD (Kuyken et al., 2001; Beck and Freeman, 1990; Young, 1994). Specifically, various theorists have suggested that individuals with PD are characterized by maladaptive cognitive processes and maladaptive behavioral strategies that make them more vulnerable to recurrent depression (e.g., Pretzer and Beck, 1996).

Given these theoretical arguments as well as the results from the current studies, the question arises as to whether MDD subjects with PD comorbidity might benefit from

treatments that combine medication with psychological interventions targeting maladaptive cognitive patterns. Although inconsistencies have emerged (e.g., Tyrer et al. 1983; Diguer et al., 1993), several studies have shown that combined therapy can be more effective than pharmacotherapy alone in depressed subjects with PD comorbidity (e.g., Bellino et al., 2006; Burnard et al., 2002; de Jonghe et al., 2001; Kool et al., 2003). In an early study, Miller et al. (1990) found that subjects with elevated cognitive biases responded better to a combined treatment with a tricyclic medication and CBT than to medication alone. More recently, Kool et al. (2003) reported that subjects with MDD-PD comorbidity improved only when treated with a combined approach involving pharmacotherapy and short psychodynamic supportive psychotherapy. In MDD subjects without PD comorbidity, the combined approach and the monotherapy had similar effects on outcome. Similarly, in a sample of MDD patients with borderline PD, Bellino et al. (2006) recently reported that a combination of fluoxetine and interpersonal psychotherapy was more effective in treating symptoms of depression and improving quality of life and interpersonal functioning than was fluoxetine alone.

Of note, the psychotherapy used in the Kool's (2003) study focused on affective, cognitive, and behavioral aspects of relationships. Similarly, in Bellino's (2006) study, the combined treatment was superior to monotherapy in ameliorating factors associated with *subjective* appraisal quality of life and dysfunctional patterns of interpersonal relationships, whereas the two treatments did not differ in their effects on global psychopathology. Collectively, these findings suggest that therapeutic interventions targeting maladaptive cognitions, interpersonal problems, and social functioning are critical for treating MDD-PD comorbidity, and the data provide important empirical

support for recent conceptualization of treatment approaches to PDs (Kuyken et al., 2001; Leichsenring and Leibing, 2003; Livesley, 2005; Pretzer and Beck, 1996).

A final comment regarding the potential implications of the present findings with respect to treatment is warranted. Recent evidence from prospective studies suggests that subjects with maladaptive cognitive patterns not only make more negative inferences in response to negative life events but also contribute significantly to the *generation* of stressful events, particularly those with interpersonal components (Safford et al., in press). Because stressful life events have been implicated in the etiology, persistence, and recurrence of depression (Brown and Harris, 1989; Kendler et al. 1999; Kessler, 1997; Tennant, 2002), treatment approaches targeting cognitive and interpersonal vulnerabilities might not only treat depression effectively but may also reduce the occurrence of stressors and, thus, decrease the likelihood of future episodes.

Implication for Etiological Models

In **Section II**, four etiological models underlying PD-depression comorbidity were described. Two of these models – the *vulnerability and pathoplasty model* – assume a temporal (causal) relation between two disorders, whereas the remaining two – *the shared factor and the spectrum model* – posit that the two comorbid disorders reflect the same etiological processes (Clark, 2005; Mineka et al., 1998). Although the design of the present studies does not enable a definitive test of these models, some methodological and conceptual comments are warranted.

First, in light of reports that a considerable percentage of MDD subjects, after being treated with antidespressants, no longer meet PD criteria (e.g., Joffe and Regan, 1988;

Fava et al., 1994, 2002; Zimmerman, 1994), only MDD subjects with a given Cluster pathology at *both* the pre- and post-treatment assessment were considered in the statistical analyses. Thus, it is parsimonious to assume that the patient's state associated with Axis I pathology had a minimal effect on PD diagnosis. More importantly, since MDD subjects with stable personality pathology were compared with MDD subjects who met no PD criteria at either assessment, we suggest that the variables mediating treatment outcome (cognitive vulnerability and stress appraisal) were primarily associated with PD rather than the state of being depressed. This speculation is further supported by the fact that several findings emerging from the present studies were specific to Cluster A, highlighting that interactions among a specific personality pathology, cognitive vulnerability, and exaggerated stress appraisal led to poorer outcome.

Second, it is important to emphasize that MDD subjects with PD showed elevated stress appraisal and depression severity after the treatment. Although conclusive statements about the causal relations between MDD and PD are not possible because the two comobid conditions were assessed concurrently, our findings provide some support for the pathoplasty model. Since premorbid assessments of cognitive, affective, and personality variables were not available, future studies should evaluate which of the two variants of the pathoplasty model – the *scar* or *complication* hypotheses – might best explain MDD-PD comorbidity.

In this framework, it is important to note that studies investigating various hypotheses of causal relations between cognitive vulnerability and depressive symptoms have yielded findings that are partially inconsistent with cognitive theories of depression (Abramson et al., 1989; Beck, 1967). In an early study, Lewinsohn et al. (1981)

compared three of these hypotheses. The first hypothesis, which was directly derived from cognitive theories of depression, states that depressive cognitions predate depression (*antecedent hypothesis*). The second hypothesis posits that depressive symptoms accompany, rather than precede, depression (*consequence hypothesis*). The third model postulates that depressive cognitions are a permanent residue of a depressive episode (*scar hypothesis*). Using a longitudinal sample, Lewinsohn et al. (1981) found no evidence to support the antecedent or scar hypotheses; the consequence hypothesis, on the other hand, was strongly supported. On the basis of these findings, the authors concluded that people who eventually became depressed did not have dysfunctional beliefs and expectancies before the depressive episode. Depressogenic cognitions did affect, however, the course of depression, since they make it more difficult to overcome a depressive episode.

In a similar vein, Oei et al. (2006) found little support for Beck's cognitive theory of depression (specifically, that changes in cognitive vulnerability are primary in the reduction of depressed mood). Using structural equation modeling and path analyses, these authors found that decreased depression severity after a 12-week CBT program led to reduced depressogenic cognitive thoughts and dysfunctional attitude. Accordingly, although there were bi-directional relations between reduction in depressive symptoms and cognitive vulnerability, depressive symptoms had a stronger impact on cognitive vulnerability than vice versa.

Moreover, evidence suggests that depressogenic cognitions might be state-dependent. Accordingly, several studies have found that dysfunctional attitudes are typically observed during depressive episodes but not after remission (e.g., Blackburn et

al., 1990; Peselow et al., 1990). These findings raise the possibility that maladaptive cognitions may be largely a function of the depressed state rather than a traitlike marker associated with vulnerability to depression. It is important to emphasize that these patterns of findings are not necessarily inconsistent with Beck's cognitive theory of depression. Indeed, Beck proposed that depressogenic schemata can remain latent in vulnerable individuals until they are activated by negative life events (Beck, 1967). Of primary relevance to the proposed studies, MDD subjects with Axis II pathology have been found to have higher levels of dysfunctional attitudes than do MDD subjects without comorbidity (Evans and Craighead, 1995; Marton et al., 1989); most importantly, Axis II pathology has been associated with depressogenic cognition even in the absence of depressive status (Hill et al., 1989; Ilardi and Craighead 1999; O'Leary et al., 1991). Based on these findings, Ilardi and Craighead (1999) concluded that "previously depressed individuals with prominent Axis II personality pathology engage in negativistic, depressogenic thought patterns in truly traitlike fashion and may thereby be more vulnerable to the experience of subsequent depressive relapse episodes" (p. 55). As we have argued in **Section III**, the chronic occurrence of distress that is characteristic of PD (APA, 2000) might help explain the traitlike nature of maladaptive cognitions in individuals with enduring personality pathology. Because depressogenic cognitions are activated by negative affect (Miranda and Persons, 1988; Miranda et al., 1990), it is possible that the chronic distress experienced by subjects with PD might continuously prime depressogenic cognitions.

When interpreted within a larger framework, the present findings underscore the need to address underlying cognitive and personality vulnerability, as well as depressive symptoms, in treatments for depression.

REFERENCES

Abramson, L.Y., Alloy, L.B., Hankin, B.L., Haeffel, G.J., Gibb, B.E., MacCoon, D.G. (2002). Cognitive vulnerability-stress models of depression in a self-regulatory and psychobiological context. In: Gotlib, I.H., Hammen C.L. (Eds.), *Handbook of Depression*. Guilford Press, New York, pp. 268-294.

Abramson, L.Y., Metalsky, G.I., Alloy, L.B. (1989). Hopelessness depression: A theory-based subtype of depression. *Psychological Review* 96, 358-372.

Abramson, L.Y., Seligman, M.E.P., Teasdale, J.D. (1978). Learned helplessness in humans: Critique and reformulation. *Journal of Abnormal Psychology* 87, 49-74.

Akiskal, H.S., Hirschfeld, R.M., Yerevanian, B.I. (1983). The relationship of personality to affective disorders. *Archives of General Psychiatry* 40, 801-810.

Akiskal, H.S., McKinney, W.T.Jr. (1973). Depressive disorders: toward a unified hypothesis. *Science* 182, 20-29.

Alloy, L.B., Abramson, L.Y., Whitehouse, W.G., Hogan, M.E., Panzarella, C., Rose, D.T. (2006). Prospective incidence of first onsets and recurrences of depression in individuals at high and low cognitive risk for depression. *Journal of Abnormal Psychology* 115, 145-156.

Alloy, L.B., Just, N., Panzarella, C. (1997). Attributional Style, Daily Life Events, and Hopelessness Depression: Subtype Validation by Prospective Variability and Specificity of Symptoms. *Cognitive Therapy and Research* 21, 321-344.

American Psychiatric Association (1980). *Diagnostic and Statistical Manual of Mental Disorders* (3rd Ed.), American Psychiatric Press, Washington, DC.

American Psychiatric Association (1987). *Diagnostic and Statistical Manual of Mental Disorders (DSM III-R).* American Psychiatric Press, Washington, DC.

American Psychiatric Association (1994). Diagnostic and Statistical Manual of Mental Disorders, (4th Ed.), American Psychiatric Press, Washington, DC.

American Psychiatric Association (2000). *Diagnostic and Statistical Manual of Mental Disorders*, (4th Ed.), American Psychiatric Press, Washington, DC.

Arbuckle, J.L. (2003). Analysis *of Moment Structures (AMOS), User's Guide version 5.0*. Small Waters Corporation, Chicago, IL.

Bagby, R.M., Joffe, R.T., Parker, J.D.A. (1993). Re-examination of the evidence for the DSM-III personality disorder clusters. *Journal of Personality Disorder* 7, 320-328.

Beach, S.R.H., Jones, D. J. (2002). Marital and family therapy for depression in adults. In: Gotlib, I.H., Hammen, C.L. (Eds.), *Handbook of Depression*. Guilford Press, New York, pp. 422-440.

Beck, A.T. (1967). *Depression: Causes and Treatment*. University of Pennsylvania Press, Philadelphia.

Beck A.T. (1983). Cognitive therapy of depression: New perspectives. In: Clayton, P.J., Barret, J.E. (Eds.), *Treatment of Depression: Old Controversies and New Approaches*. Raven Press, New York, pp. 265-290.

Beck, A.T., Freeman, A. Davis, D.D. and Associates (1990). *Cognitive Therapy for Personality Disorders*. Guilford Press, New York.

Beck, A.T., Rush, A., Shaw, B., Emery, G. (1979). *Cognitive Therapy of Depression.* Guilford Press, New York.

Beck, A.T., Steer, R.A., Kovacs, M., Garrison, B. (1985). Hopelessness and eventual suicide: a 10-year prospective study of patients hospitalized with suicidal ideation. *American Journal of Psychiatry* 142, 559-563.

Bellino, S., Zizza, M., Rinaldi, C., Bogetto, F. (2006). Combined treatment of major depression in patients with borderline personality disorder: a comparison with pharmacotherapy. *Canadian Journal of Psychiatry* 51, 453-460.

Bentler, P.M. (1990). Comparative fit indexes in structural models. *Psychological Bulletin* 107, 238-246.

Bielski, R.J., Friedel, R.O. (1976). Prediction of tricyclic antidepressant response: a critical review. *Archives of General Psychiatry* 33, 1479-1489.

Bifulco, A., Bernazzani, O., Moran, P.M., Ball, C. (2000). Lifetime stressors and recurrent depression: preliminary findings of the Adult Life Phase Interview (ALPHI). *Social Psychiatry and Psychiatric Epidemiology* 35, 264-275.

Black, D.W., Bell, S., Hulbert, J., Nasrallah, A. (1988). The importance of Axis II in patients with major depression. A controlled study. *Journal of Affective Disorders* 14, 115-122.

Blais, M.A. (1997). Clinician ratings of the five-factor model of personality and the DSM-IV personality disorders. *The Journal of Nervous and Mental Disease* 185, 388-393.

Blatt S.J. (1974). Levels of object representation in anaclitic and introjective depression. *The Psychoanalytic Study of the Child* 29, 107-157.

Blatt, S.J. (1991). A cognitive morphology of psychopathology. *Journal of Nervous and Mental Disease* 179, 449-458.

Blatt, S.J., D'Afflitti, J.P., Quinlan, D.M. (1976). Experiences of depression in normal young adults. *Journal of Abnormal Psychology* 85, 383-389.

Blatt, S.J., Quinlan, D.M., Chevron, E.S., McDonald, C., Zuroff, D. (1982). Dependency and self-criticism: psychological dimensions of depression. *Journal of Consulting and Clinical Psychology* 50, 113-124.

Blatt, S.J., Quinlan, D.M., Pilkonis, P.A., Shea, M.T. (1995). Impact of perfectionism and need for approval on the brief treatment of depression: the National Institute of Mental Health Treatment of Depression Collaborative Research Program revisited. *Journal of Consulting and Clinical Psychology* 63, 125-132. Erratum in: *Journal of Consulting and Clinical Psychology* 1995, 63, 494.

Blatt, S.J., Shichman, S. (1983). Two primary configurations of psychopathology. *Psychoanalysis and Contemporary Thought, 6,* 187-254.

Blazer, D.G., Kessler, R.C., McGonagle, K.A., Swartz, M.S. (1994). The prevalence and distribution of major depression in a national community sample: the National Comorbidity Survey. *American Journal of Psychiatry* 151, 979-986.

Bolger, N, Schilling, E.A. (1991). Personality and the problems of everyday life: the role of neuroticism in exposure and reactivity to daily stressors. *Journal of Personality* , 59, 355-386.

Bolger, N., Zuckerman, A. (1995). A framework for studying personality in the stress process. *Journal of Personality and Social Psychology* 69, 890-902.

Brieger, P., Ehrt, U., Bloeink, R., Marneros, A. (2002). Consequences of comorbid personality disorders in major depression. *Journal of Nervous Mental Disorders* 190, 304-309.

Brieger, P., Ehrt, U., Marneros, A. (2003). Frequency of comorbid personality disorders in bipolar and unipolar affective disorders. *Comprehensive Psychiatry* 44, 28-34.

Brown, G. W., Harris, T. O. (1989). *Life Events and Illness*. Guilford Press, New York.

Brown, G.P., Hammen, C.L., Craske, M.G., Wickens, T.D. (1995). Dimensions of dysfunctional attitudes as vulnerabilities to depressive symptoms. *Journal of Abnormal Psychology* 104, 431-435.

Brown, G.W., Harris, T.O. (1978). *The Social Origins of Depression: A Study of Psychiatric Disorder in Women*. Tavistock Press, London, UK.

Browne, M.W., Cudeck, R. (1993). Alternative ways of assessing model fit. In: Bollen K.A., Long, J.S. (Eds.), *Testing Structural Equation Models*. Sage Publications, Newbury Park, CA, pp. 136-162.

Burnand, Y., Andreoli, A., Kolatte, E., Venturini, A., Rosset, N. (2002). Psychodynamic psychotherapy and clomipramine in the treatment of major depression. *Psychiatric Services* 53, 585-590.

Butzlaff, R.L., Hooley, J.M. (1998). Expressed emotion and psychiatric relapse: a meta-analysis. *Archives of General Psychiatry* 55, 547-552.

Cairney, J., Boyle, M., Offord, D.R., Racine, Y. (2003). Stress, social support and depression in single and married mothers. *Social Psychiatry and Psychiatric Epidemiology* 38, 442-449.

Camisa, K.M., Bockbrader, M.A., Lysaker, P., Rae, L.L., Brenner, C.A., O'Donnell, B.F. (2005). Personality traits in schizophrenia and related personality disorders. *Psychiatry Research* 133, 23-33.

Carmines, E., McIver, J. (1981). Analyzing models with unobserved variables: Analysis of covariance structures. In: Bohrnstedt G., Borgatta, E. (Eds.), *Social Measurement: Current Issues*. Sage Publications, Beverly Hills, CA, pp. 65-115.

Casey, P., Birbeck, G., McDonagh, C., Horgan, A., Dowrick, C., Dalgard, O., Lethinen, V., Ayuso-Mateos, J. L., Dunn, G., Page, H., Wilkinson, C., Wilkinson, G., Vazquez-Barquero, J. L. (2004). Personality disorder, depression and functioning: results from the ODIN study. *Journal of Affective Disorders* 82, 277-283.

Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A., Poulton, R. (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 301, 386-389.

Church, N.F., Brechman-Toussaint, M.L., Hine, D.W. (2005). Do dysfunctional cognitions mediate the relationship between risk factors and postnatal depression symptomatology? *Journal of Affective Disorders* 87, 65-72.

Clark, L.A. (2005). Temperament as a unifying basis for personality and psychopathology. *Journal of Abnormal Psychology* 114, 505-521.

Clark, L.A., Vorhies, L., McEwen, J.L. (1994). Personality disorder symptomatology from the five-factor model perspective. In: Costa, P.T.Jr., Widiger, T.A. (Eds.), *Personality Disorders and the Five-Factor Model of Personality.* American Psychological Association, Washington, DC, pp. 95-117.

Clark, L.A., Watson, D. (1991). Tripartite model of anxiety and depression: psychometric evidence and taxonomic implications. *Journal of Abnormal Psychology* 100, 316-336.

Cohen, S., Kamarck, T., Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior* 24, 385-396.

Cohen, S., Williamson, G. (1988). Perceived stress in a probability sample of the United States. In: Spacapan, S., Oskamp, S. (Eds.), *The Social Psychology of Health: Claremont Symposium on Applied Social Psychology*. Sage Publications, Newbury Park, CA, pp. 31-67.

Coolidge, F.L., Becker, L.A., DiRito, D.C., Durham, R.L., Kinlaw, M.M., Philbrick, P.B. (1994). On the relationship of the five-factor personality model to personality disorders: four reservations. *Psychological Reports* 75, 11-21.

Corruble, E, Ginestet, D., Guelfi, J.D. (1996). Comorbidity of personality disorders and unipolar major depression: a review. *Journal of Affective Disorders* 37, 157-170.

Costa, P.T. Jr, McCrae, R.R. (2005). A Five-Factor Model perspective on personality disorders. In: Strack, S. (Ed.), *Handbook of Personology and Psychopathology*. John Wiley & Sons Press, Hoboken, NJ, pp. 257-270.

Costa, P.T., McCrae, R.R. (1990). Personality disorders and the five-factor model of personality. *Journal of Personality Disorders* 4, 362-371.

Coyne, J.C., Whiffen, V.E. (1995). Issues in personality as diathesis for depression: the case of sociotropy-dependency and autonomy-self-criticism. *Psychological Bulletin* 118, 358-378.

Cyranowski, J.M., Frank, E., Winter, E., Rucci, P., Novick, D., Pilkonis, P., Fagiolini, A., Swartz, H.A., Houck, P., Kupfer, D.J. (2004). Personality pathology and outcome in recurrently depressed women over 2 years of maintenance interpersonal psychotherapy. *Psychological Medicine* 34, 659-669.

Daley, S.E., Hammen, C., Burge, D. (1999). Depression and Axis II symptomatology in an adolescent community sample: Concurrent and longitudinal associations. *Journal of Personality Disorder* 13, 47-59.

Daley, S.E., Hammen, C., Davila, J., Burge, D. (1998). Axis II symptomatology, depression, and life stress during the transition from adolescence to adulthood. *Journal of Consulting and Clinical Psychology* 66, 595-603.

Daley, S.E., Hammen, C., Rao, U. (2000). Predictors of first onset and recurrence of major depression in young women during the 5 years following high school graduation. *Journal of Abnormal Psychology* 109, 525-533.

Daley, S.E., Hammen, C., Burge, D., Davila, J., Paley, B., Lindberg, N., Herzberg, D. (1997). Predictors of the generation of stressful life events: A longitudinal study of late adolescent women. *Journal of Abnormal Psychology, 106,* 251-259.

Davila, J., Hammen, C., Burge, D., Paley, B., Daley, S.E. (1995). Poor interpersonal problem solving as a mechanism of stress generation in depression among adolescent women. *Journal of Abnormal Psychology* 104, 592-600.

de Jonghe, F., Kool, S., van Aalst, G., Dekker, J., Peen, J. (2001). Combining psychotherapy and antidepressants in the treatment of depression. *Journal of Affective Disorders* 64, 217-229.

Diguer, L., Barber, J.P., Luborsky, L. (1993). Three concomitants: personality disorders, psychiatric severity, and outcome of dynamic psychotherapy of major depression. *American Journal of Psychiatry* 150, 1246-1248.

Dohrenwend, B.P., Levav, I., Shrout, P.E., Schwartz, S., Naveh, G., Link, B.G., Skodol, A.E., Stueve, A. (1992). Socioeconomic status and psychiatric disorders: the causation-selection issue. *Science* 255, 946-952.

Dunkley, D.M., Blankstein, K.R., Halsall, J., Williams, M., Winkworth, G. (2000). The relation between perfectionism and distress: hassles, coping, and perceived social support as mediators and moderators. *Journal of Consulting and Clinical Psychology* 47, 437-453.

Dunkley, D.M., Sanislow, C.A., Grilo, C.M., McGlashan, T.H. (2006). Perfectionism and depressive symptoms 3 years later: negative social interactions, avoidant coping, and perceived social support as mediators. *Comprehensive Psychiatry* 47, 106-115.

Dunkley, D.M., Zuroff, D.C., Blankstein, K.R. (2003). Self-critical perfectionism and daily affect: dispositional and situational influences on stress and coping. *Journal of Personality and Social Psychology* 84, 234-252.

Dyce, J.A., O'Connor, B.P. (1998). Personality disorders and the five-factor model: a test of facet-level predictions. *Journal of Personality Disorder* 12, 31-45.

Dykman, B.M, Johll, M. (1998). Dysfunctional attitudes and vulnerability to depressive symptoms: A 14-week longitudinal study. *Cognitive Therapy and Research* 22, 337-352.

Ehlert, U., Gaab, J., Heinrichs, M. (2001). Psychoneuroendocrinological contributions to the etiology of depression, posttraumatic stress disorder, and stress-related bodily disorders: the role of the hypothalamus-pituitary-adrenal axis. *Biological Psychology* 57, 141-152.

Ehnvall, A., Agren, H. (2002). Patterns of sensitisation in the course of affective illness. A life-charting study of treatment-refractory depressed patients. *Journal of Affective Disorders* 70, 67-75.

Ensel, W.M., Peek, M.K., Lin, N., Lai, G. (1996). Stress in the life course: a life history approach. *Journal of Aging and Health* 8, 389-416.

Eysenck, H.J. (1990). Biological dimensions of personality. In: Pervin, L.A. (Ed.), *Handbook of Personality: Theory and Research*. Guilford Press, New York, pp. 244-276.

Eysenck, H.J., Eysenck, M.W. (1985). *Personality and individual differences: A natural science approach.* Plenum Press, New York.

Ezquiaga, E., Garcia, A., Bravo, F., Pallares, T. (1998). Factors associated with outcome in major depression: a 6-month prospective study. *Social Psychiatry and Psychiatry Epidemiology* 33, 552-557.

Farabaugh, A., Mischoulon, D., Yeung, A., Alpert, J., Matthews, J., Pava, J., Fava, M. (2002). Predictors of stable personality disorder diagnoses in outpatients with remitted depression. *Journal of Nervous Mental Disorders* 190, 248-256.

Farabaugh, A.H., Sonawalla, S.B., Fava, M., Pedrelli, P., Papakostas, G.I., Schwartz, F., Mischoulon, D. (2006). Differences in cognitive factors between "true drug" versus "placebo pattern" response to fluoxetine as defined by pattern analysis. *Human Psychopharmacology* 21, 221-225.

Fava, M., Bless, E., Otto, M.W., Pava, J.A., Rosenbaum, J.F. (1994). Dysfunctional attitudes in major depression. Changes with pharmacotherapy. *Journal of Nervous Mental Disorders* 182, 45-49.

Fava, M., Bouffides, E., Pava, J.A., McCarthy, M.K., Steingard, R.J., Rosenbaum, JF. (1994). Personality disorder comorbidity with major depression and response to fluoxetine treatment. *Psychotherapy and Psychosomatics* 62, 160-167.

Fava, M., Farabaugh, A.H., Sickinger, A.H. (2002). Personality disorders and depression. *Psychological Medicine* 32, 1049-1057.

Fava, M., Farabaugh, A.H., Sickinger, A.H., Wright, E., Alpert, J.E., Sonawalla, S., Nierenberg, A.A., Worthington, J.J 3rd. (2002). Personality disorders and depression. *Psychological Medicine* 32, 1049-1057.

Fava, M., Kendler, K.S. (2000). Major depressive disorder. *Neuron* 28, 335-341.

Fava, M., Littman, A., Halperin, P., Pratt, E., Drews, F. R., Oleshansky, M., Knapik, J., Thompson, C., Bielenda, C. (1991). Psychological and behavioral benefits of a stress/type A behavior reduction program for healthy middle-aged army officers. *Psychosomatics* 32, 337-342.

Fava, M., Rosenbaum, J.F., McCarthy, M. (1992). Correlations between perceived stress and depressive symptoms among depressive outpatients. *Stress Medicine* 8, 73-76.

Fava, M., Uebelacker, L.A, Alpert, J.E, Nierenberg, A.A, Pava, J.A., Rosenbaum, J. F. (1997). Major depressive subtypes and treatment response. *Biological psychiatry* 42, 568-576.

Fennell, M.J., Campbell, E.A. (1984). The cognitions questionnaire: specific thinking errors in depression. *British Journal of Clinical Psychology* 23, 81-92.

Fergusson, D.M., Horwood, L.J., Lynskey, M.T. (1997). The effects of unemployment on psychiatric illness during young adulthood. *Psychological Medicine* 27, 371-381.

First, M.B., Spitzer, R.L., Gibbon M., and Williams, J.B.W., Janet B.W. (1997). *Structured Clinical Interview for DSM-IV Personality Disorders, (SCID-II).* American Psychiatric Press, Inc.,Washington, D.C.

Flett, G.L., Hewitt, P.L., Blankstein, K.R. (1995). Perfectionism, life events, and depressive symptoms: A test of a diathesis-stress model. *Current Psychology* 14, 112-137.

Gold, P.W., Chrousos, G.P. (2002). Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. *Molecular Psychiatry* 7, 254-275.

Goldberg, J.O., Segal, Z.V., Vella, D.D. (1989). Depressive personality: Millon Clinical Multiaxial Inventory profiles of sociotropic and autonomous subtypes. *Journal of Personality Disorders* 3, 193-198.

Gotlib, I., Hammen, C. (2002). *Handbook of Depression.* Guilford Press, New York.

Grant, B.F., Hasin, D.S., Stinson, F.S., Dawson, D.A., Chou, S.P., Ruan, W.J., Pickering, R.P. (2004). Prevalence, correlates, and disability of personality disorders in the United States: results from the national epidemiologic survey on alcohol and related conditions. *Journal of Clinical Psychiatry* 65, 948-958.

Grazioli, R., Terry, D.J. (2000). The role of cognitive vulnerability and stress in the prediction of postpartum depressive symptomatology. *British Journal of Clinical Psychology* 39, 329-347.

Greden, J.F. (2001). The burden of disease for treatment-resistant depression. *The Journal of Clinical Psychiatry* 62, 26-31.

Grilo, C.M., Sanislow, C.A., Shea, M.T., Skodol, A.E., Stout, R.L., Gunderson, J.G., Yen, S., Bender, D.S., Pagano, M.E., Zanarini, M.C., Morey, L.C., McGlashan, T.H. (2005). Two-year prospective naturalistic study of remission from major depressive disorder as a function of personality disorder comorbidity. *Journal of Consulting and Clinical Psychology* 73, 78-85.

Gunderson, J.G, Ronningstam, E. (2001). Differentiating narcissistic and antisocial personality disorders. *Journal of Personality Disorders* 15, 103-109.

Gurrera, R.J., Dickey, C.C., Niznikiewicz, M.A., Voglmaier, M.M., Shenton, M.E., McCarley, R.W. (2005). The five-factor model in schizotypal personality disorder. *Schizophrenia Research* 80, 243-251.

Haaga, D.A., Dyck, M.J., Ernst, D. (1991). Empirical status of cognitive theory of depression. *Psychological Bulletin* 110, 215-236.

Haffel, G.J., Abramson, L.Y., Voelz, Z.R., Metalsky, G.I., Halberstadt, L., Dykman, B.M., Donovan, P., Hogan, M.E., Hankin, B.L., Alloy, L.B. (2005). Negative cognitive styles, dysfunctional attitudes, and the remitted depression paradigm: a search for the elusive cognitive vulnerability to depression factor among remitted depressives. *Emotion* 5, 343-348.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry* 23, 56-62.

Hammen, C. (1991). Generation of stress in the course of unipolar depression. *Journal of Abnormal Psychology* 100, 555-561.

Hammen, C. (2005). Stress and depression. *Annual Review of Clinical Psychology* 1, 293-319.

Hammen, C., Brennan, P.A. (2002). Interpersonal dysfunction in depressed women: impairments independent of depressive symptoms. *Journal of Affective Disorders* 72, 145-156.

Hammen, C., Davila, J., Brown, G., Ellicott, A., Gitlin, M. (1992). Psychiatric history and stress: predictors of severity of unipolar depression. *Journal of Abnormal Psychology* 101, 45-52.

Hammen, C., Henry, R., Daley, S.E. (2000). Depression and sensitization to stressors among young women as a function of childhood adversity. *Journal of Consulting and Clinical Psychology* 68, 782-787

Hammen, C., Marks, T., Mayol, A., deMayo, R. (1985). Depressive self-schemas, life stress, and vulnerability to depression. *Journal of Abnormal Psychology* 94, 308-319.

Hankin, B.L., Abramson, L.Y., Miller, N. (2004). Cognitive vulnerability-stress theories of depression: Examining affective specificity in the prediction of depression versus anxiety in three prospective studies. *Cognitive Therapy and Research* 28, 309-345.

Hankin, B.L., Fraley, R.C., Abela, J.R. (2005). Daily depression and cognitions about stress: evidence for a traitlike depressogenic cognitive style and the prediction of depressive symptoms in a prospective daily diary study. *Journal of Personality and Social Psychology* 88, 673-685.

Harkness, K.L, Luther, J. (2001). Clinical risk factors for the generation of life events in major depression. *Journal of Abnormal Psychology* 110, 564-572.

Harkness, K.L., Monroe, S.M., Simons, A.D., Thase, M. (1999). The generation of life events in recurrent and non-recurrent depression. *Psychological Medicine* 29, 135-144.

Harris, T.O., Borsanyi, S., Messari, S., Stanford, K., Cleary, S.E., Shiers, H.M., Brown, G.W., Herbert, J. (2000). Morning cortisol as a risk factor for subsequent major depressive disorder in adult women. *The British Journal of Psychiatry* 177, 505-510.

Hart, A. B., Craighead, W. E. & Craighead, L. W. (2001). Predicting recurrence of major depressive disorder in young adults: a prospective study. *Journal of Abnormal Psychology* 110, 633-643.

Hayes, A.M., Castonguay, L.G., Goldfried, M.R. (1996). Effectiveness of targeting the vulnerability factors of depression in cognitive therapy. *Journal of Consulting and Clinical Psychology* 64, 623-627.

Heim, C., Plotsky, P.M., Nemeroff, C.B. (2004). Importance of studying the contributions of early adverse experience to neurobiological findings in depression. *Neuropsychopharmacology* 29, 641-648.

Heinrichs, M., Baumgartner, T., Kirschbaum, C., Ehlert, U. (2003). Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. *Biological Psychiatry* 54, 1389-1398.

Hewitt, P.L., Flett, G.L., Ediger, E. (1996). Perfectionism and depression: longitudinal assessment of a specific vulnerability hypothesis. *Journal of Abnormal Psychology* 105, 276-280.

Hill, C.V., Oei, T.P., Hill, M.A. (1989). An empirical investigation of the specificity and sensitivity of the Automatic Thoughts Questionnaire and Dysfunctional Attitudes Scale. *Journal of Psychopathology and Behavioral Assessment* 11, 291-311.

Holsboer F. (1995). Neuroendocrinology of mood disorders. In: Bloom, F.E, Kupfer, D.J. (Eds.), *Psychopharmacology: The Fourth Generation in Progress*. Raven Press, New York, pp 957-969.

Hooley, J.M., Teasdale, J.D. (1989). Predictors of relapse in unipolar depressives: expressed emotion, marital distress, and perceived criticism. *Journal of Abnormal Psychology* 98, 229-235.

Hoyle, R.H., Panter, A.T. (1995). Writing about structural equation models. In Hoyle, R.H. (Ed.), *Structural Equation Modeling*. Sage Publications, Thousand Oaks, CA, pp.158-176.

Iacoviello, B.M., Alloy, L.B., Abramson, L.Y., Whitehouse, W.G., Hogan, M.E. (2006). The course of depression in individuals at high and low cognitive risk for depression: a prospective study. *Journal of Affective Disorders* 93, 61-69.

Ilardi, S.S., Craighead, W.E. (1999). The relationship between personality pathology and dysfunctional cognitions in previously depressed adults. *Journal of Abnormal Psychology* 108, 51-57.

Ilardi, S.S., Craighead, W.E., Evans, D.D. (1997). Modeling relapse in unipolar depression: the effects of dysfunctional cognitions and personality disorders. *Journal of Consulting and Clinical Psychology* 65, 381-391.

Ingram, R.E., Miranda, J., Segal, Z.V. (1998). *Cognitive Vulnerability to Depression*. Guilford Press, New York.

Jacobs, N., Kenis, G., Peeters, F., Derom, C., Vlietinck, R., van-Os, J. (2006). Stress-related negative affectivity and genetically altered serotonin transporter function:

evidence of synergism in shaping risk of depression. *Archives of General Psychiatry* 63, 989-996.

James, W. (1981). *The Principles of Psychology*. Harvard University Press, Cambridge, MA. Originally published in 1890.

Jarrett, R.B, Eaves, G.G, Grannemann, B.D, Rush, A.J. (1991). Clinical, cognitive, and demographic predictors of response to cognitive therapy for depression: a preliminary report. *Psychiatry Research* 37, 245-260.

Joffe, R.T., Regan, J.J. (1988). Personality and depression. *Psychiatric Research* 22, 279-286.

Joiner, T.E., Metalsky, G.I., Lew, A., Klocek, J. (1999). Testing the causal mediation component of Beck's theory of depression: Evidence for specific mediation. *Cognitive Therapy and Research* 23, 401-412.

Kaufman, J., Yang, B.Z., Douglas-Palumberi, H., Houshyar, S., Lipschitz, D., Krystal, J.H., Gelernter, J. (2004). Social supports and serotonin transporter gene moderate depression in maltreated children. *Proceedings of the National Academy of Sciences of the United States of America* 101, 17316-17321.

Keith, T.Z. (2006). *Multiple Regression and Beyond*. Pearson Education, Inc., Boston.

Keller, M.B., Boland, R.J. (1998). Implications of failing to achieve successful long-term maintenance treatment of recurrent unipolar major depression. *Biological Psychiatry* 44, 348-360.

Kendler, K.S, Karkowski, L.M., Prescott, C.A. (1999). Causal relationship between stressful life events and the onset of major depression. *American Journal of Psychiatry* 156, 837-841.

Kendler, K.S., Gardner, C.O., Prescott, C.A. (2003). Personality and the experience of environmental adversity. *Psychological Medicine* 33, 1193-1202.

Kendler, K.S., Gatz, M., Gardner, C.O., Pedersen, N.L. (2006). Personality and major depression: a Swedish longitudinal, population-based twin study. *Archives of General Psychiatry* 63, 1113-1120.

Kendler, K.S., Karkowski, L.M., Prescott, C.A. (1998). Stressful life events and major depression: risk period, long-term contextual threat, and diagnostic specificity. *Journal of Nervous and Mental Disease* 186, 661-669.

Kendler, K.S., Kuhn, J., Prescott, C.A. (2004). The interrelationship of neuroticism, sex, and stressful life events in the prediction of episodes of major depression. *American Journal of Psychiatry* 161, 631-636.

Kendler, K.S., Roy, M.A. (1995). Validity of a diagnosis of lifetime major depression obtained by personal interview versus family history. *American Journal of Psychiatry* 152, 1608-1614.

Kendler, K.S., Thornton, L.M., Gardner, C.O. (2001). Genetic risk, number of previous depressive episodes, and stressful life events in predicting onset of major depression. *American Journal of Psychiatry* 158, 582-586.

Kessler, R.C. (1997). The effects of stressful life events on depression. *Annual review of psychology* 48, 191-214.

Kessler, R.C., Berglund, P., Demler, O., Jin, R., Merikangas, K.R., Walters, E.E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry* 62, 593–602.

Klein, D.N. (2003). Patients' versus informants' reports of personality disorders in predicting 7 1/2-year outcome in outpatients with depressive disorders. *Psychological Assessment* 15, 216-222.

Klocek, J.W., Oliver J.M., Ross M.J. (1997). The role of dysfunctional attitudes, negative life events, and social support in the prediction of depressive dysphoria: A prospective longitudinal study. *Social Behavior and Personality* 25, 123-136.

Kool, S., Dekker, J., Duijsens, I.J., de Jonghe, F., Puite, B. (2003). Efficacy of combined therapy and pharmacotherapy for depressed patients with or without personality disorders. *Harvard Review of Psychiatry*; 11, 133-141.

Kool, S., Schoevers, R., De Maat, S., Van, R., Molenaar, P., Vink, A., Dekker, J. (2005). Efficacy of pharmacotherapy in depressed patients with and without personality disorders: a systematic review and meta-analysis. *Journal of Affective Disorders* 88, 269-278.

Kuyken, W., Kurzer, N., DeRubeis, R.J., Beck, A.T., Brown, G.K. (2001). Response to cognitive therapy in depression: the role of maladaptive beliefs and personality disorders. *Journal of Consulting and Clinical Psychology* 69, 560-566.

Lazarus, R.S., Folkman, S. (1984). *Stress, Appraisal and Coping*. Springer Publishing Company, New York.

Lee, A.L., Ogle, W.O., Sapolsky, R.M. (2002). Stress and depression: possible links to neuron death in the hippocampus. *Bipolar Disorders* 4, 117-128.

Leichsenring, F., Leibing, E. (2003). The effectiveness of psychodynamic therapy and cognitive behavior therapy in the treatment of personality disorders: a meta-analysis. *American Journal of Psychiatry* 160, 1223-1232.

Lewinsohn, P.M., Joiner, T.E. Jr, Rohde, P. (2001). Evaluation of cognitive diathesis-stress models in predicting major depressive disorder in adolescents. *Journal of Abnormal Psychology* 110, 203-215.

Lewinsohn, P.M., Mischel, W., Chaplin, W., Barton, R. (1980). Social competence and depression: the role of illusory self-perceptions. *Journal of Abnormal Psychology* 89, 203-212.

Lewinsohn, P.M., Steinmetz, J.L., Larson, D.W., Franklin, J. (1981). Depression-related cognitions: antecedent or consequence? *Journal of Abnormal Psychology* 90, 213-219.

Livesley, W.J. (1986). Trait and behavioral prototypes of personality disorder. *American Journal of Psychiatry* 143, 728-732.

Livesley, W.J. (1987). A systematic approach to the delineation of personality disorder. *American Journal of Psychiatry* 144, 772-777.

Livesley, W.J. (2005). Principles and strategies for treating personality disorder. *Canadian Journal of Psychiatry* 50, 442-450.

Livesley, W.J., Jackson, D.N. (1991). Construct validity and the classification of personality disorders. In: Oldham, J. (Ed.), *Personality Disorders. New Perspectives on Diagnostic Validity.* American Psychiatric Association, Washington, DC.

Livesley, W.J., Jackson, D.N. (1992). Guidelines for developing, evaluating, and revising the classification of personality disorders. *Journal of Nervous and Mental Disease* 180, 609-618.

Livesley, W.J., Schroeder, M.L. (1991). Dimensions of personality disorder. The DSM-III-R cluster B diagnoses. *Journal of Nervous and Mental Disease* 179, 317-328.

Livesley, W.J., Schroeder, M.L., Jackson, D.N., Jang, K.L. (1994). Categorical distinctions in the study of personality disorder: implications for classification. *Journal of Abnormal Psychology* 103, 6-17.

Luty, S.E., Joyce, P.R., Mulder, R.T., Sullivan, P.F., McKenzie, J.M. (1999). The relationship of dysfunctional attitudes to personality in depressed patients. *Journal of Affective Disorders* 54, 75-80.

Lynch, T.R., Mendelson, T., Robins, C.J., Krishnan, K.R., George, L.K., Johnson, C.S., Blazer, D.G. (1999). Perceived social support among depressed elderly, middle-aged, and young-adult samples: cross-sectional and longitudinal analyses. *Journal of Affective Disorders* 55, 159-170.

MacLeod, A.K., Williams, J.M. (1990) Overgeneralization: an important but non-homogeneous construct. *British Journal of Clinical Psychology* 29, 443-444.

Magnus, K., Diener, E., Fujita, F., Pavot, W. (1993). Extraversion and neuroticism as predictors of objective life events: a longitudinal analysis. *Journal of Personality and Social Psychology* 65, 1046-1053.

Marton, P., Korenblum, M., Kutcher, S., Stein, B., Kennedy, B., Pakes, J. (1989). Personality dysfunction in depressed adolescents. *Canadian Journal of Psychiatry* 34, 810-813.

Mazure, C.M. (1998). Life Stressors as Risk Factors in Depression. *Clinical Psychology: Science and Practice* 5, 291-313.

Mazure, C.M., Bruce, M.L., Maciejewski, P.K., Jacobs, S.C. (2000). Adverse life events and cognitive-personality characteristics in the prediction of major depression and antidepressant response. *American Journal of Psychiatry* 157, 896-903.

Mazure, C.M., Maciejewski, P.K., Jacobs, S.C., Bruce, M.L. (2002). Stressful life events interacting with cognitive/personality styles to predict late-onset major depression. *American Journal of Geriatric Psychiatry* 10, 297-304.

McGonagle, K.A., Kessler, R.C. (1990). Chronic stress, acute stress, and depressive symptoms. *American journal of community psychology* 18, 681-706.

McQuaid, J.R., Monroe, S.M., Roberts, J.E., Kupfer, D.J., Frank, E. (2000). A comparison of two life stress assessment approaches: prospective prediction of treatment outcome in recurrent depression. *Journal of Abnormal Psychology* 109, 787-791.

Metalsky, G.I., Joiner, T.E. Jr, Hardin, T.S., Abramson, L.Y. (1993). Depressive reactions to failure in a naturalistic setting: a test of the hopelessness and self-esteem theories of depression. *Journal of Abnormal Psychology* 102, 101-109.

Meyers, B.S., Sirey, J.A., Bruce, M., Hamilton, M., Raue, P., Friedman, S.J., Rickey, C., Kakuma, T., Carroll, M.K., Kiosses, D., Alexopoulos, G. (2002). Predictors of early recovery from major depression among persons admitted to community-based clinics: an observational study. *Archives of General Psychiatry* 59, 729-735.

Miller, J.D., Pilkonis, P.A. (2006). Neuroticism and affective instability: the same or different? *American Journal of Psychiatry* 163, 839-345.

Miller, IW, Norman, W.H, Keitner, G.I. (1990). Treatment response of high cognitive dysfunction depressed inpatients. *Comprehensive Psychiatry* 31, 62-71

Millon, T. (1981). *Disorders of Personality: DSM-III, Axis II.* John Wiley & Sons Press, New York.

Mineka, S., Watson, D., Clark, L.A. (1998). Comorbidity of anxiety and unipolar mood disorders. *Annual Review of Psychology* 49, 377-412.

Miranda, J., Persons, J.B. (1988). Dysfunctional attitudes are mood-state dependent. *Journal of Abnormal Psychology* 97, 76-79.

Miranda, J., Persons, J.B., Byers, C.N. (1990). Endorsement of dysfunctional beliefs depends on current mood state. *Journal of Abnormal Psychology* 99, 237-241.

Mitchell, S, Campbell, E.A. (1988). Cognitions associated with anxiety and depression. *Personality and Individual Differences* 9, 837-838.

Mitropoulou, V., Goodman, M., Sevy, S., Elman, I., New, A.S., Iskander, E.G., Silverman, J.M., Breier, A., Siever, L.J. (2004). Effects of acute metabolic stress on the dopaminergic and pituitary-adrenal axis activity in patients with schizotypal personality disorder. *Schizophrenia Research* 70, 27-31.

Mongrain, M., Blackburn, S. (2005). Cognitive Vulnerability, Lifetime Risk, and the Recurrence of Major Depression in Graduate Students. *Cognitive Therapy and Research* 29, 747-768.

Monroe, S.M., Hadjiyannakis, K. (2002). The social environment and depression: Focusing on severe life stress. In: Gotlib, I.H., Hammen, C.L. (Eds.), *Handbook of Depression*. Guilford Press, New York, pp.314-340.

Moran, P., Rendu, A., Jenkins, R., Tylee, A., Mann, A. (2001). The impact of personality disorder in UK primary care: a 1-year follow-up of attenders. *Psychological Medicine* 31, 1447-1454.

Morey, L.C., Gunderson, J., Quigley, B.D., Lyons, M. (2000). Dimensions and categories: the "big five" factors and the DSM personality disorders. *Assessment 7,* 203-216.

Morey, L.C., Gunderson, J.G., Quigley, B.D., Shea, M.T., Skodol, A.E., McGlashan, T.H., Stout, R.L., Zanarini, M.C. (2002). The representation of borderline, avoidant, obsessive-compulsive, and schizotypal personality disorders by the five-factor model. *Journal of Personality Disorders* 16, 215-234.

Morse, J.Q., Pilkonis, P.A., Houck, P.R., Frank, E., Reynolds, C.F. 3rd. (2005). Impact of cluster C personality disorders on outcomes of acute and maintenance treatment in late-life depression. *American Journal of Geriatric Psychiatry* 13, 808-814.

Mulder, R. (2006). Personality disorder and outcome in depression. *British Journal of Psychiatry* 189, 186-187.

Mulder, R.T. (2002). Personality pathology and treatment outcome in major depression: a review. *American Journal of Psychiatry* 159, 359-371.

Mulder, R.T., Joyce, P.R., Frampton, C.M., Luty, S.E., Sullivan, P.F. (2006). Six months of treatment for depression: outcome and predictors of the course of illness. *The American Journal of Psychiatry* 163, 95-100.

Mulder, R.T., Joyce, P.R., Luty, S.E. (2003). The relationship of personality disorders to treatment outcome in depressed outpatients. *Journal of Clinical Psychiatry* 64, 259-264.

Munafo, M.R., Clark, T.G., Roberts, K.H., Johnstone, E.C. (2006). Neuroticism mediates the association of the serotonin transporter gene with lifetime major depression. *Neuropsychobiology* 53, 1-8.

Murray, C.J., Lopez, A.D. (1996). Evidence-based health policy--lessons from the Global Burden of Disease Study. *Science* 274, 740-743.

Newton-Howes, G., Tyrer, P., Johnson, T. (2006). Personality disorder and the outcome of depression: meta-analysis of published studies. *British Journal of Psychiatry* 188, 13-20.

Nolen-Hoeksema, S., Ahrens, C. (2002). Age differences and similarities in the correlates of depressive symptoms. *Psychology and Aging* 17, 116-124.

Oei, T.P., Bullbeck, K., Campbell, J.M. (2006). Cognitive change process during group cognitive behaviour therapy for depression. *Journal of Affective Disorders* 92, 231-241.

O'Leary, K.M., Cowdry, R.W., Gardner, D.L. (1991). Dysfunctional attitudes in borderline personality disorder. *Journal of Personality Disorders* 5, 233-242.

Ormel, J., Wohlfarth, T. (2006). How neuroticism, long-term difficulties, and life situation change influence psychological distress: a longitudinal model. *Journal of Personality and Social Psychology* 60, 744-755.

Ouimette, P.C., Klein, D.N., Anderson, R., Riso, L.P., Lizardi, H. (1994). Relationship of sociotropy/autonomy and dependency/self-criticism to DSM-III-R personality disorders. *Journal of Abnormal Psychology* 103, 743-749.

Ouimette, P.C., Klein, D.N., Pepper, C.M. (1996). Personality traits in the first degree relatives of outpatients with depressive disorders. *Journal of Affective Disorders* 39, 43-53.

Patience, D.A., McGuire, R.J., Scott, A.I., Freeman, C.P. (1995). The Edinburgh Primary Care Depression Study: personality disorder and outcome. *The British Journal of Psychiatry* 167, 324-330.

Patton, G.C., Coffey, C., Posterino, M., Carlin, J.B., Bowes, G. (2003). Life events and early onset depression: cause or consequence? *Psychological Medicine* 33, 1203-1210.

Paykel, E.S. (1994). Life events, social support and depression. *Acta Psychiatrica Scandinavia (Supplement)* 377, 50-58.

Paykel E.S, Cooper Z. (1992). Life events and social stress. In: Paykel, E.S. (2nd Ed.), *Handbook of Affective Disorders*. Churchill Livingstone, London, UK, pp. 149-170.

Pepper, C.M, Klein, D.N., Anderson, R.L., Riso, L.P., Ouimette, P.C., Lizardi, H. (1995). DSM-III-R axis II comorbidity in dysthymia and major depression. *American Journal of Psychiatry* 152, 239-247.

Peselow, E.D., Fieve, R.R., DiFiglia, C. (1992). Personality traits and response to desipramine. *Journal of Affective Disorders* 24, 209-216.

Peselow, E.D., Robins, C., Block, P., Barouche, F., Fieve, R.R. (1990). Dysfunctional attitudes in depressed patients before and after clinical treatment and in normal control subjects. *American Journal of Psychiatry* 147, 439-444.

Pfohl, B., Stangl, D., Zimmerman, M. (1984). The implications of DSM-III personality disorders for patients with major depression. *Journal of Affective Disorders* 7, 309-318.

Pilkonis, P.A., Frank, E. (1988). Personality pathology in recurrent depression: nature, prevalence, and relationship to treatment response. *American Journal of Psychiatry* 145, 435-41.

Pilkonis, P. (1988). Personality prototypes among depressives: Themes of dependency and autonomy. *Journal of Personality Disorders, 2,* 144-152.

Post, R.M. (1992). Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *American Journal of Psychiatry* 149, 999-1010.

Poulton, R.G., Andrews, G. (1992). Personality as a cause of adverse life events. *Acta Psychiatrica Scandinavica* 85, 35-38.

Pretzer, J.L., Beck, A.T. (1996). A Cognitive Theory of Personality Disorders. In Clarkin, J. (Ed.), *Major Theories of Personality Disorder*. Guilford Press, New York, pp. 36-105.

Reich, J.H., Green, A.I. (1991). Effect of personality disorders on outcome of treatment. *The Journal of Nervous and Mental Disease* 179, 74-82.

Reilly-Harrington, N.A., Alloy, L.B., Fresco, D.M., Whitehouse, W.G. (1999). Cognitive styles and life events interact to predict bipolar and unipolar symptomatology. *Journal of Abnormal Psychology* 108, 567-578.

Riso, L.P., du Toit, P.L., Blandino, J.A., Penna, S., Dacey, S., Duin, J.S., Pacoe, E.M., Grant, M.M., Ulmer, C.S. (2003). Cognitive aspects of chronic depression. *Journal of Abnormal Psychology* 112, 72-80.

Riso, L.P., Klein, D.N., Ferro, T., Kasch, K.L., Pepper, C.M., Schwartz, J.E., Aronson, T.A. (1996). Understanding the comorbidity between early-onset dysthymia and

cluster B personality disorders: a family study. *American Journal of Psychiatry* 153, 900-906.

Riso, L.P., Miyatake, R.K., Thase, M.E. (2002). The search for determinants of chronic depression: a review of six factors. *Journal of affective disorders* 70, 103-115.

Roberts, S.B., Kendler, K.S. (1999). Neuroticism and self-esteem as indices of the vulnerability to major depression in women. *Psychological Medicine* 29, 1101-1109.

Romanov, K., Varjonen, J., Kaprio, J., Koskenvuo, M. (2003). Life events and depressiveness - the effect of adjustment for psychosocial factors, somatic health and genetic liability. *Acta Psychiatrica Scandinavica* 107, 25-33.

Russell, J.M., Kornstein, S.G., Shea, M.T., McCullough, J.P., Harrison, W.M., Hirschfeld, R.M., Keller, M. B. (2003). Chronic depression and comorbid personality disorders: response to sertraline versus imipramine. *The Journal of Clinical Psychiatry* 64, 554-561.

Russell, J.M., Kornstein, S.G., Shea, M.T., McCullough, J.P., Harrison, W.M., Hirschfeld, R.M., Keller, M.B. (2003). Chronic depression and comorbid personality disorders: response to sertraline versus imipramine. *Journal of Clinical Psychiatry* 64, 554-561.

Safford, S.M., Alloy, L.B., Abramson, L.Y, Crossfield, A.G. (in press). Negative cognitive style as a predictor of negative life events in depression-prone individuals: A test of the stress generation hypothesis. *Journal of Affective Disorders*.

Sareen, J., Enns, M.W., Guertin, J.E. (2000). The impact of clinically diagnosed personality disorders on acute and one-year outcomes of electroconvulsive therapy. *Journal of ECT* 16, 43-51.

Sartorius, N. (2001). The economic and social burden of depression. *The Journal of Clinical Psychiatry* 62, 8-11.

Sato, T., Sakado, K., Sato, S. (1993). Is there any specific personality disorder or personality disorder cluster that worsens the short-term treatment outcome of major depression? *Acta Psychiatrica Scandinavica* 88, 342-349.

Sato, T., Sakado, K., Sato, S., Morikawa, T. (1994). Cluster A personality disorder: a marker of worse treatment outcome of major depression? *Psychiatry Research* 53, 153-159.

Scott, J., Harrington, J. (1996). A preliminary study of the relationship among personality, cognitive vulnerability, symptom profile, and outcome in major depressive disorder. *Journal of Nervous and Mental Diseases* 184, 503-505.

Scott, J., Williams, J.M., Brittlebank, A., Ferrier, I.N. (1995). The relationship between premorbid neuroticism, cognitive dysfunction and persistence of depression: a 1-year follow-up. *Journal of Affective Disorders* 33, 167-172.

Segal, Z.V., Shaw, B.F., Vella, D.D., Katz, R. (1992). Cognitive and life stress predictors of relapse in remitted unipolar depressed patients: test of the congruency hypothesis. *Journal of Abnormal Psychology* 101, 26-36.

Seivewright, H., Tyrer, P., Johnson, T. (2004). Persistent social dysfunction in anxious and depressed patients with personality disorder. *Acta Psychiatrica Scandinavica* 109, 104-109.

Seligman, M.E. (1972) Learned helplessness. *Annual Review of Medicine* 23, 207-412.

Shahar, G., Blatt, S.J., Zuroff, D.C., Pilkonis, P.A. (2003). Role of perfectionism and personality disorder features in response to brief treatment for depression. *Journal of Consulting and Clinical Psychology* 71, 629-633.

Shea, M.T, Widiger, T.A., Klein, M.H. (1992). Comorbidity of personality disorders and depression: implications for treatment. *Journal of Consulting and Clinical Psychology* 60, 857-868.

Shea, M.T., Pilkonis, P.A., Beckham, E., Collins, J.F., Elkin, I., Sotsky, S.M., Docherty, J.P. (1990). Personality disorders and treatment outcome in the NIMH Treatment of Depression Collaborative Research Program. *American Journal of Psychiatry* 147, 711-718.

Shedler, J., Westen, D. (2004). Refining personality disorder diagnosis: integrating science and practice. *American Journal of Psychiatry* 161, 1350-1365.

Siever, L.J., Davis, K.L. (1985). Overview: toward a dysregulation hypothesis of depression. *American Journal of Psychiatry* 142, 1017-1031.

Siever, L.J., Davis, K.L. (1991). A psychobiological perspective on the personality disorders. *American Journal of Psychiatry* 148, 1647-1658.

Skodol, A.E, Grilo, C.M, Pagano, M.E, Bender, D.S, Gunderson, J.G, Shea, M.T, Yen, S., Zanarini, M.C., McGlashan, T.H. (2005). Effects of personality disorders on functioning and well-being in major depressive disorder. *Journal of Psychiatric Practice* 11, 363-368.

Skodol, A.E., Oldham, J.M., Bender, D.S., Dyck, I.R., Stout, R.L., Morey, L.C., Shea, M.T., Zanarini, M.C., Sanislow, C.A., Grilo, C.M., McGlashan, T.H., Gunderson, J.G. (2005). Dimensional representations of DSM-IV personality disorders:

relationships to functional impairment. *American Journal of Psychiatry* 162, 1919-1925.

Sobel, M.E. (1982). Asymptotic intervals for indirect effects in structural equations models. In Leinhart, S. (Ed), *Sociological Methodology*. Jossey-Bass, San Francisco, pp.290-312.

Spitzer, R.L, Williams, J.B.W., Gibbon, M., First, M. B. (1989). *Structured Clinical Interview for DSM-III-R – Patient Edition*. Biometrics Research Department, New York State Psychiatric Institute, New York.

Taylor, S.E., Way, B.M., Welch, W.T., Hilmert, C.J., Lehman, B.J., Eisenberger, N.I. (2006). Early family environment, current adversity, the serotonin transporter promoter polymorphism, and depressive symptomatology. *Biological Psychiatry* 60, 671-676.

Tennant, C. (2002). Life events, stress and depression: a review of recent findings. *Australian and New Zealand Journal of Psychiatry* 36, 173-182.

Thase M., Jindal R., Howland R. (2002). Biological Aspects of depression. In: Gotlib, I., Hammen, C. (Eds.), *Handbook of Depression.* Guilford Press, New York, pp. 192-218.

Thase, M.E., Simons, A.D., McGeary, J., Cahalane, J.F., Hughes, C., Harden, T., Friedman, E. (1992). Relapse after cognitive behavior therapy of depression: potential implications for longer courses of treatment. *American Journal of Psychiatry* 149, 1046-1052.

Thompson, L.W., Gallagher, D., Czirr, R. (1988). Personality disorder and outcome in the treatment of late-life depression. *American Journal of Geriatric Psychiatry* 21, 133-153.

Trivedi, M.H., Rush, A.J., Wisniewski, S.R., Nierenberg, A.A., Warden, D., Ritz, L., Norquist, G., Howland, R.H., Lebowitz, B., McGrath, P.J., Shores-Wilson, K., Biggs, M.M., Balasubramani, G.K., Fava, M., STAR*D Study Team (2006). Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *American Journal of Psychiatry* 163, 28-40.

Trull, T. J., Durrett, C.A. (2005). Categorical and dimensional models of personality Disorder. *Annual Review of Clinical Psychology* 1, 355-380.

Tyrer, P., Seivewright, N., Ferguson, B., Murphy, S. & Johnson, A. L. (1993). The Nottingham Study of Neurotic Disorder: effect of personality status on response to drug treatment, cognitive therapy and self-help over two years. *British Journal of Psychiatry* 162, 219-226.

Uchino, B.N. (2006). Social support and health: a review of physiological processes potentially underlying links to disease outcomes. *Journal of Behavioral Medicine* 29, 377-387.

Ustun, T.B., Chisholm, D. (2001). Global "burden of disease"-study for psychiatric disorders. *Psychiatrische Praxis* 28, 7-11.

Van Praag, H.M. (2004). Can stress cause depression? *Progress in Neuropsychopharmacology and Biological Psychiatry* 28, 891-907.

Van-Os, J., Jones, P.B. (1999). Early risk factors and adult person--environment relationships in affective disorder. *Psychological Medicine* 29, 1055-1067.

Wade, T.D., Kendler, K.S. (2000). The relationship between social support and major depression: cross-sectional, longitudinal, and genetic perspectives. *The Journal of Nervous and Mental Disease* 188, 251-258.

Ward, R.K. (2004). Assessment and Management of Personality Disorders. *American Family Physician* 70, 1505-1512.

Weissman, A.N., Beck, A.T. (1978, November). Development and validation of the Dysfunctional Attitude Scale (DAS). Paper presented at the 12th annual meeting of the Association for the Advancement of Behavior Therapy, Chicago, IL.

Weissman, M.M., Prusoff, B.A., Klerman, G.L. (1978). Personality and the prediction of long-term outcome of depression. *American Journal of Psychiatry* 135, 797-800.

Whisman, M.A., Uebelacker, L.A., Weinstock, L.M. (2004). Psychopathology and marital satisfaction: the importance of evaluating both partners. *Journal of Consulting and Clinical Psychology* 72, 830-838.

Widiger, T.A., Clark, L.A. (2000). Toward DSM-V and the classification of psychopathology. *Psychological Bulletin* 126, 946-963.

Yen, S., McDevitt-Murphy, M.E., Shea, M.T. (2005). Depression and personality. In: Stein, D.J., Kupfer, D.J., Schatzberg, A.F. (Eds.), *The American Psychiatric Publishing Textbook of Mood Disorders*. American Psychiatric Publishing, Inc., Washington, DC, pp. 673-686.

Young, E.A., Lopez, J.F., Murphy-Weinberg, V., Watson, S.J., Akil, H. (2000). Hormonal evidence for altered responsiveness to social stress in major depression. *Neuropsychopharmacology* 23, 411-418.

Young, J. E. (1994). *Cognitive Therapy for Personality Disorders: A Schema-Focused Approach* (2nd edn). Professional Resource Press, Sarasota, FL.

Ystgaard, M., Tambs, K., Dalgard, O.S. (1999). Life stress, social support and psychological distress in late adolescence: A longitudinal study. *Social Psychiatry and Psychiatric Epidemiology* 34, 12-19.

Zimmerman, M. (1994). Diagnosing personality disorders. A review of issues and research methods. *Archives of General Psychiatry* 51, 225-245.

Zuroff, D.C., Blatt, S.J. (2002). Vicissitudes of life after the short-term treatment of depression: Roles of stress, social support, and personality. *Journal of Social and Clinical Psychology* 21, 473-496.

Zuroff, D.C., Blatt, S.J., Sanislow, C.A. 3rd, Bondi, C.M., Pilkonis, P.A. (1999). Vulnerability to depression: reexamining state dependence and relative stability. *Journal of Abnormal Psychology* 108, 76-89.

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